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(57) Abstract

The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

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**NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED
HUMAN G PROTEIN-COUPLED RECEPTORS**

This patent application is a continuation-in-part of, and claims priority from, U.S. Serial Number 09/170,496, filed with the United States Patent and Trademark Office on
5 October 13, 1998. This application also claims the benefit of priority from the following provisional applications, all filed via U.S. Express Mail with the United States Patent and Trademark Office on the indicated dates: U.S. Provisional Number 60/110,060, filed November 27, 1998; U.S. Provisional Number 60/120,416, filed February 16, 1999; U.S. Provisional Number 60/121,852, filed February 26, 1999 claiming benefit of U.S.
10 Provisional Number 60/109,213, filed November 20, 1998; U.S. Provisional Number 60/123,944, filed March 12, 1999; U.S. Provisional Number 60/123,945, filed March 12, 1999; U.S. Provisional Number 60/123,948, filed March 12, 1999; U.S. Provisional Number 60/123,951, filed March 12, 1999; U.S. Provisional Number 60/123,946, filed March 12, 1999; U.S. Provisional Number 60/123,949, filed March 12, 1999; U.S.
15 Provisional Number 60/152,524, filed September 3, 1999, claiming benefit of U.S. Provisional Number 60/151,114, filed August 27, 1999 and U.S. Provisional Number 60/108,029, filed November 12, 1998; U.S. Provisional Number 60/136,436, filed May 28, 1999; U.S. Provisional Number 60/136,439, filed May 28, 1999; U.S. Provisional Number 60/136,567, filed May 28, 1999; U.S. Provisional Number 60/137,127, filed May 28,
20 1999; U.S. Provisional Number 60/137,131, filed May 28, 1999; U.S. Provisional Number

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60/141,448, filed June 29, 1999 claiming benefit of U.S. Provisional Number 60/136,437, filed May 28, 1999; U.S. Provisional Number 60/156,633, filed September 29, 1999; U.S. Provisional Number 60/156,555, filed September 29, 1999; U.S. Provisional Number 60/156,634, filed September 29, 1999; U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: CHN10-1), filed September 29, 1999; U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: RUP6-1), filed October 1, 1999; U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: RUP7-1), filed October 1, 1999; U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: CHN6-1), filed October 1, 1999; U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: RUP5-1), filed October 1, 1999; and U.S. Provisional Number ____ (Arena Pharmaceuticals, Inc. docket number: CHN9-1), filed October 1, 1999. This application is also related to co-pending U.S. Serial Number ____ (Woodcock, Washburn, Kurtz, Makiewicz & Norris, LLP docket number AREN-0050), filed on October 12, 1999 (via U.S. Express Mail) and U.S. Serial Number 09/364,425, filed on July 30, 1999, both incorporated herein by reference. This application also claims priority to U.S. Serial Number ____ (Woodcock, Washburn, Kurtz, Makiewicz & Norris, LLP docket number AREN-0054), filed on October 12, 1999 (via U.S. Express Mail), incorporated by reference herein in its entirety. Each of the foregoing applications are incorporated by reference herein in their entirety.

20

FIELD OF THE INVENTION

The invention disclosed in this patent document relates to transmembrane receptors, and more particularly to human G protein-coupled receptors, and specifically to

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GPCRs that have been altered to establish or enhance constitutive activity of the receptor. Preferably, the altered GPCRs are used for the direct identification of candidate compounds as receptor agonists, inverse agonists or partial agonists having potential applicability as therapeutic agents.

5

BACKGROUND OF THE INVENTION

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR or GPCRs) class. It is estimated that there are some 100,000 genes within the human genome, and of these, approximately 2%, or 2,000 genes, are estimated to code for GPCRs. Receptors, including GPCRs, for which the endogenous ligand has been identified are referred to as "known" receptors, while receptors for which the endogenous ligand has not been identified are referred to as "orphan" receptors. GPCRs represent an important area for the development of pharmaceutical products: from approximately 20 of the 100 known GPCRs, 60% of all prescription pharmaceuticals have been developed.

15

GPCRs share a common structural motif. All these receptors have seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane (each span is identified by number, *i.e.*, transmembrane-1 (TM-1), transmembrane-2 (TM-2), etc.). The transmembrane helices are joined by strands of amino acids between transmembrane-2 and transmembrane-3, transmembrane-4 and transmembrane-5, and transmembrane-6 and transmembrane-7 on the exterior, or "extracellular" side, of the cell membrane (these are referred to as "extracellular" regions 1, 2 and 3 (EC-1, EC-2 and EC-3), respectively). The transmembrane helices are also joined by strands of amino acids between transmembrane-1 and transmembrane-2, transmembrane-3 and transmembrane-4, and

20

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transmembrane-5 and transmembrane-6 on the interior, or "intracellular" side, of the cell membrane (these are referred to as "intracellular" regions 1, 2 and 3 (IC-1, IC-2 and IC-3), respectively). The "carboxy" ("C") terminus of the receptor lies in the intracellular space within the cell, and the "amino" ("N") terminus of the receptor lies in the extracellular space
5 outside of the cell.

Generally, when an endogenous ligand binds with the receptor (often referred to as "activation" of the receptor), there is a change in the conformation of the intracellular region that allows for coupling between the intracellular region and an intracellular "G-protein." It has been reported that GPCRs are "promiscuous" with respect to G proteins, *i.e.*,
10 that a GPCR can interact with more than one G protein. *See, Kenakin, T., 43 Life Sciences* 1095 (1988). Although other G proteins exist, currently, Gq, Gs, Gi, Gz and Go are G proteins that have been identified. Endogenous ligand-activated GPCR coupling with the G-protein begins a signaling cascade process (referred to as "signal transduction"). Under normal conditions, signal transduction ultimately results in cellular activation or cellular inhibition.
15 It is thought that the IC-3 loop as well as the carboxy terminus of the receptor interact with the G protein.

Under physiological conditions, GPCRs exist in the cell membrane in equilibrium between two different conformations: an "inactive" state and an "active" state. A receptor in an inactive state is unable to link to the intracellular signaling transduction
20 pathway to produce a biological response. Changing the receptor conformation to the active state allows linkage to the transduction pathway (via the G-protein) and produces a biological response.

A receptor may be stabilized in an active state by an endogenous ligand or a

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compound such as a drug. Recent discoveries, including but not exclusively limited to modifications to the amino acid sequence of the receptor, provide means other than endogenous ligands or drugs to promote and stabilize the receptor in the active state conformation. These means effectively stabilize the receptor in an active state by
5 simulating the effect of an endogenous ligand binding to the receptor. Stabilization by such ligand-independent means is termed "constitutive receptor activation."

SUMMARY OF THE INVENTION

Disclosed herein are non-endogenous versions of endogenous, human GPCRs and uses thereof.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a representation of 8XCRE-Luc reporter plasmid (*see*, Example 4(c)3.)

Figures 2A and 2B are graphic representations of the results of ATP and ADP binding to endogenous TDAG8 (2A) and comparisons in serum and serum free media (2B).

15

Figure 3 is a graphic representation of the comparative signaling results of CMV versus the GPCR Fusion Protein H9(F236K):Gsa.

DETAILED DESCRIPTION

The scientific literature that has evolved around receptors has adopted a number of terms to refer to ligands having various effects on receptors. For clarity and
20 consistency, the following definitions will be used throughout this patent document. To the extent that these definitions conflict with other definitions for these terms, the following definitions shall control:

AGONISTS shall mean materials (*e.g.*, ligands, candidate compounds) that

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activate the intracellular response when they bind to the receptor, or enhance GTP binding to membranes.

AMINO ACID ABBREVIATIONS used herein are set out in Table A:

| TABLE A | | | |
|---------|---------------|-----|---|
| 5 | ALANINE | ALA | A |
| | ARGININE | ARG | R |
| | ASPARAGINE | ASN | N |
| | ASPARTIC ACID | ASP | D |
| | CYSTEINE | CYS | C |
| 10 | GLUTAMIC ACID | GLU | E |
| | GLUTAMINE | GLN | Q |
| | GLYCINE | GLY | G |
| | HISTIDINE | HIS | H |
| | ISOLEUCINE | ILE | I |
| 15 | LEUCINE | LEU | L |
| | LYSINE | LYS | K |
| | METHIONINE | MET | M |
| | PHENYLALANINE | PHE | F |
| | PROLINE | PRO | P |
| 20 | SERINE | SER | S |
| | THREONINE | THR | T |
| | TRYPTOPHAN | TRP | W |
| | TYROSINE | TYR | Y |
| | VALINE | VAL | V |

25 **PARTIAL AGONISTS** shall mean materials (*e.g.*, ligands, candidate compounds) that activate the intracellular response when they bind to the receptor to a lesser degree/extent than do agonists, or enhance GTP binding to membranes to a lesser degree/extent than do agonists.

ANTAGONIST shall mean materials (*e.g.*, ligands, candidate compounds) that
 30 competitively bind to the receptor at the same site as the agonists but which do not activate the intracellular response initiated by the active form of the receptor, and can thereby inhibit the intracellular responses by agonists or partial agonists. **ANTAGONISTS** do not diminish the baseline intracellular response in the absence of an agonist or partial agonist.

CANDIDATE COMPOUND shall mean a molecule (for example, and not limitation,

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a chemical compound) that is amenable to a screening technique. Preferably, the phrase "candidate compound" does not include compounds which were publicly known to be compounds selected from the group consisting of inverse agonist, agonist or antagonist to a receptor, as previously determined by an indirect identification process ("indirectly identified
5 compound"); more preferably, not including an indirectly identified compound which has previously been determined to have therapeutic efficacy in at least one mammal; and, most preferably, not including an indirectly identified compound which has previously been determined to have therapeutic utility in humans.

COMPOSITION means a material comprising at least one component; a
10 "pharmaceutical composition" is an example of a composition.

COMPOUND EFFICACY shall mean a measurement of the ability of a compound to inhibit or stimulate receptor functionality, as opposed to receptor binding affinity. Exemplary means of detecting compound efficacy are disclosed in the Example section of this patent document.

15 **CODON** shall mean a grouping of three nucleotides (or equivalents to nucleotides) which generally comprise a nucleoside (adenosine (A), guanosine (G), cytidine (C), uridine (U) and thymidine (T)) coupled to a phosphate group and which, when translated, encodes an amino acid.

CONSTITUTIVELY ACTIVATED RECEPTOR shall mean a receptor subject to
20 constitutive receptor activation. A constitutively activated receptor can be endogenous or non-endogenous.

CONSTITUTIVE RECEPTOR ACTIVATION shall mean stabilization of a receptor in the active state by means other than binding of the receptor with its endogenous

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ligand or a chemical equivalent thereof.

CONTACT or **CONTACTING** shall mean bringing at least two moieties together, whether in an in vitro system or an in vivo system.

DIRECTLY IDENTIFYING or **DIRECTLY IDENTIFIED**, in relationship to the
5 phrase "candidate compound", shall mean the screening of a candidate compound against a constitutively activated receptor, preferably a constitutively activated orphan receptor, and most preferably against a constitutively activated G protein-coupled cell surface orphan receptor, and assessing the compound efficacy of such compound. This phrase is, under no circumstances, to be interpreted or understood to be encompassed by or to encompass the
10 phrase "indirectly identifying" or "indirectly identified."

ENDOGENOUS shall mean a material that a mammal naturally produces. **ENDOGENOUS** in reference to, for example and not limitation, the term "receptor," shall mean that which is naturally produced by a mammal (for example, and not limitation, a human) or a virus. By contrast, the term **NON-ENDOGENOUS** in this context shall mean
15 that which is not naturally produced by a mammal (for example, and not limitation, a human) or a virus. For example, and not limitation, a receptor which is not constitutively active in its endogenous form, but when manipulated becomes constitutively active, is most preferably referred to herein as a "non-endogenous, constitutively activated receptor." Both terms can be utilized to describe both "in vivo" and "in vitro" systems. For example, and not limitation,
20 in a screening approach, the endogenous or non-endogenous receptor may be in reference to an in vitro screening system. As a further example and not limitation, where the genome of a mammal has been manipulated to include a non-endogenous constitutively activated receptor, screening of a candidate compound by means of an in vivo system is viable.

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G PROTEIN COUPLED RECEPTOR FUSION PROTEIN and GPCR FUSION PROTEIN, in the context of the invention disclosed herein, each mean a non-endogenous protein comprising an endogenous, constitutively activate GPCR or a non-endogenous, constitutively activated GPCR fused to at least one G protein, most preferably the alpha (α) subunit of such G protein (this being the subunit that binds GTP), with the G protein preferably being of the same type as the G protein that naturally couples with endogenous orphan GPCR. For example, and not limitation, in an endogenous state, if the G protein "G α " is the predominate G protein that couples with the GPCR, a GPCR Fusion Protein based upon the specific GPCR would be a non-endogenous protein comprising the GPCR fused to G α ; in some circumstances, as will be set forth below, a non-predominant G protein can be fused to the GPCR. The G protein can be fused directly to the c-terminus of the constitutively active GPCR or there may be spacers between the two.

HOST CELL shall mean a cell capable of having a Plasmid and/or Vector incorporated therein. In the case of a prokaryotic Host Cell, a Plasmid is typically replicated as a autonomous molecule as the Host Cell replicates (generally, the Plasmid is thereafter isolated for introduction into a eukaryotic Host Cell); in the case of a eukaryotic Host Cell, a Plasmid is integrated into the cellular DNA of the Host Cell such that when the eukaryotic Host Cell replicates, the Plasmid replicates. Preferably, for the purposes of the invention disclosed herein, the Host Cell is eukaryotic, more preferably, mammalian, and most preferably selected from the group consisting of 293, 293T and COS-7 cells.

INDIRECTLY IDENTIFYING or INDIRECTLY IDENTIFIED means the traditional approach to the drug discovery process involving identification of an endogenous ligand specific for an endogenous receptor, screening of candidate compounds against the

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receptor for determination of those which interfere and/or compete with the ligand-receptor interaction, and assessing the efficacy of the compound for affecting at least one second messenger pathway associated with the activated receptor.

INHIBIT or **INHIBITING**, in relationship to the term "response" shall mean that a
5 response is decreased or prevented in the presence of a compound as opposed to in the absence of the compound.

INVERSE AGONISTS shall mean materials (*e.g.*, ligand, candidate compound) which bind to either the endogenous form of the receptor or to the constitutively activated form of the receptor, and which inhibit the baseline intracellular response initiated by the
10 active form of the receptor below the normal base level of activity which is observed in the absence of agonists or partial agonists, or decrease GTP binding to membranes. Preferably, the baseline intracellular response is inhibited in the presence of the inverse agonist by at least 30%, more preferably by at least 50%, and most preferably by at least 75%, as compared with the baseline response in the absence of the inverse agonist.

15 **KNOWN RECEPTOR** shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has been identified.

LIGAND shall mean an endogenous, naturally occurring molecule specific for an endogenous, naturally occurring receptor.

MUTANT or **MUTATION** in reference to an endogenous receptor's nucleic acid
20 and/or amino acid sequence shall mean a specified change or changes to such endogenous sequences such that a mutated form of an endogenous, non-constitutively activated receptor evidences constitutive activation of the receptor. In terms of equivalents to specific sequences, a subsequent mutated form of a human receptor is considered to be equivalent to

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a first mutation of the human receptor if (a) the level of constitutive activation of the subsequent mutated form of a human receptor is substantially the same as that evidenced by the first mutation of the receptor; and (b) the percent sequence (amino acid and/or nucleic acid) homology between the subsequent mutated form of the receptor and the first mutation
5 of the receptor is at least about 80%, more preferably at least about 90% and most preferably at least 95%. Ideally, and owing to the fact that the most preferred cassettes disclosed herein for achieving constitutive activation includes a single amino acid and/or codon change between the endogenous and the non-endogenous forms of the GPCR, the percent sequence homology should be at least 98%.

10 **NON-ORPHAN RECEPTOR** shall mean an endogenous naturally occurring molecule specific for an endogenous naturally occurring ligand wherein the binding of a ligand to a receptor activates an intracellular signaling pathway.

ORPHAN RECEPTOR shall mean an endogenous receptor for which the endogenous ligand specific for that receptor has not been identified or is not known.

15 **PHARMACEUTICAL COMPOSITION** shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the
20 needs of the artisan.

PLASMID shall mean the combination of a Vector and cDNA. Generally, a Plasmid is introduced into a Host Cell for the purposes of replication and/or expression of the cDNA as a protein.

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STIMULATE or **STIMULATING**, in relationship to the term "response" shall mean that a response is increased in the presence of a compound as opposed to in the absence of the compound.

VECTOR in reference to cDNA shall mean a circular DNA capable of incorporating
5 at least one cDNA and capable of incorporation into a Host Cell.

The order of the following sections is set forth for presentational efficiency and is not intended, nor should be construed, as a limitation on the disclosure or the claims to follow.

A. Introduction

The traditional study of receptors has always proceeded from the a priori assumption
10 (historically based) that the endogenous ligand must first be identified before discovery could proceed to find antagonists and other molecules that could affect the receptor. Even in cases where an antagonist might have been known first, the search immediately extended to looking for the endogenous ligand. This mode of thinking has persisted in receptor research even after the discovery of constitutively activated receptors. What has not been heretofore recognized
15 is that it is the active state of the receptor that is most useful for discovering agonists, partial agonists, and inverse agonists of the receptor. For those diseases which result from an overly active receptor or an under-active receptor, what is desired in a therapeutic drug is a compound which acts to diminish the active state of a receptor or enhance the activity of the receptor, respectively, not necessarily a drug which is an antagonist to the endogenous ligand.
20 This is because a compound that reduces or enhances the activity of the active receptor state need not bind at the same site as the endogenous ligand. Thus, as taught by a method of this invention, any search for therapeutic compounds should start by screening compounds against the ligand-independent active state.

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B. Identification of Human GPCRs

The efforts of the Human Genome project has led to the identification of a plethora of information regarding nucleic acid sequences located within the human genome; it has been the case in this endeavor that genetic sequence information has been made available without an understanding or recognition as to whether or not any particular genomic sequence does or may contain open-reading frame information that translate human proteins. Several methods of identifying nucleic acid sequences within the human genome are within the purview of those having ordinary skill in the art. For example, and not limitation, a variety of human GPCRs, disclosed herein, were discovered by reviewing the GenBank™ database, while other GPCRs were discovered by utilizing a nucleic acid sequence of a GPCR, previously sequenced, to conduct a BLAST™ search of the EST database. Table B, below, lists several endogenous GPCRs that we have discovered, along with a GPCR's respective homologous receptor.

TABLE B

| | Disclosed Human Orphan GPCRs | Accession Number Identified | Open Reading Frame (Base Pairs) | Per Cent Homology To Designated GPCR | Reference To Homologous GPCR (Accession No.) |
|----|------------------------------|-----------------------------|---------------------------------|--------------------------------------|--|
| 15 | hARE-3 | AL033379 | 1,260 bp | 52.3% LPA-R | U92642 |
| 20 | hARE-4 | AC006087 | 1,119 bp | 36% P2Y5 | AF000546 |
| | hARE-5 | AC006255 | 1,104 bp | 32% <i>Oryzias latipes</i> | D43633 |
| | hGPR27 | AA775870 | 1,128 bp | | |
| | hARE-1 | AI090920 | 999 bp | 43% KIAA0001 | D13626 |
| | hARE-2 | AA359504 | 1,122 bp | 53% GPR27 | |
| 25 | hPPR1 | H67224 | 1,053 bp | 39% EBI1 | L31581 |
| | hG2A | AA754702 | 1,113 bp | 31% GPR4 | L36148 |

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| | | | | | |
|----|---------------|-------------|----------|---|--|
| | hRUP3 | AL035423 | 1,005 bp | 30% <i>Drosophila</i> | 2133653 |
| | | | | <i>melanogaster</i> | |
| | hRUP4 | AI307658 | 1,296 bp | 32% pNPGPR 28% and 29 % <i>Zebra fish</i> Ya and Yb, respectively | NP_004876 AAC41276 and AAB94616 |
| | hRUP5 | AC005849 | 1,413 bp | 25% DEZ 23% FMLPR | Q99788 P21462 |
| | hRUP6 | AC005871 | 1,245 bp | 48% GPR66 | NP_006047 |
| 5 | hRUP7 | AC007922 | 1,173 bp | 43% H3R | AF140538 |
| | hCHN3 | EST 36581 | 1,113 bp | 53% GPR27 | |
| | hCHN4 | AA804531 | 1,077 bp | 32% thrombin | 4503637 |
| | hCHN6 | EST 2134670 | 1,503 bp | 36% edg-1 | NP_001391 |
| | hCHN8 | EST 764455 | 1,029 bp | 47% KIAA0001 | D13626 |
| 10 | hCHN9 | EST 1541536 | 1,077 bp | 41% LTB4R | NM_000752 |
| | hCHN10 | EST 1365839 | 1,055 bp | 35% P2Y | NM_002563 |

Receptor homology is useful in terms of gaining an appreciation of a role of the receptors within the human body. As the patent document progresses, we will disclose techniques for mutating these receptors to establish non-endogenous, constitutively activated

15 versions of these receptors.

The techniques disclosed herein have also been applied to other human, orphan GPCRs known to the art, as will be apparent as the patent document progresses.

C. Receptor Screening

Screening candidate compounds against a non-endogenous, constitutively activated

20 version of the human GPCRs disclosed herein allows for the direct identification of candidate compounds which act at this cell surface receptor, without requiring use of the receptor's endogenous ligand. By determining areas within the body where the endogenous version of human GPCRs disclosed herein is expressed and/or over-expressed, it is possible to determine related disease/disorder states which are associated with the expression and/or over-expression

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of the receptor; such an approach is disclosed in this patent document.

With respect to creation of a mutation that may evidence constitutive activation of the human GPCR disclosed herein is based upon the distance from the proline residue at which is presumed to be located within TM6 of the GPCR; this algorithmic technique is disclosed
5 in co-pending and commonly assigned patent document U.S. Serial Number 09/170,496, incorporated herein by reference. The algorithmic technique is not predicated upon traditional sequence "alignment" but rather a specified distance from the aforementioned TM6 proline residue. By mutating the amino acid residue located 16 amino acid residues from this residue (presumably located in the IC3 region of the receptor) to, most preferably, a lysine residue,
10 such activation may be obtained. Other amino acid residues may be useful in the mutation at this position to achieve this objective.

D. Disease/Disorder Identification and/or Selection

As will be set forth in greater detail below, most preferably inverse agonists to the non-endogenous, constitutively activated GPCR can be identified by the methodologies of this
15 invention. Such inverse agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor. Because of the ability to directly identify inverse agonists to the GPCR, thereby allowing for the development of pharmaceutical compositions, a search for diseases and disorders associated with the GPCR is relevant. For example, scanning both diseased and normal tissue samples for the presence
20 of the GPCR now becomes more than an academic exercise or one which might be pursued along the path of identifying an endogenous ligand to the specific GPCR. Tissue scans can be conducted across a broad range of healthy and diseased tissues. Such tissue scans provide a preferred first step in associating a specific receptor with a disease and/or disorder. *See, for*

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example, co-pending application (docket number ARE-0050) for exemplary dot-blot and RT-PCR results of several of the GPCRs disclosed herein.

Preferably, the DNA sequence of the human GPCR is used to make a probe for (a) dot-blot analysis against tissue-mRNA, and/or (b) RT-PCR identification of the expression
5 of the receptor in tissue samples. The presence of a receptor in a tissue source, or a diseased tissue, or the presence of the receptor at elevated concentrations in diseased tissue compared to a normal tissue, can be preferably utilized to identify a correlation with a treatment regimen, including but not limited to, a disease associated with that disease. Receptors can equally well be localized to regions of organs by this technique. Based on
10 the known functions of the specific tissues to which the receptor is localized, the putative functional role of the receptor can be deduced.

E. Screening of Candidate Compounds

1. Generic GPCR screening assay techniques

When a G protein receptor becomes constitutively active, it binds to a G protein (*e.g.*,
15 Gq, Gs, Gi, Gz, Go) and stimulates the binding of GTP to the G protein. The G protein then acts as a GTPase and slowly hydrolyzes the GTP to GDP, whereby the receptor, under normal conditions, becomes deactivated. However, constitutively activated receptors continue to exchange GDP to GTP. A non-hydrolyzable analog of GTP, [³⁵S]GTPγS, can be used to monitor enhanced binding to membranes which express constitutively activated receptors.
20 It is reported that [³⁵S]GTPγS can be used to monitor G protein coupling to membranes in the absence and presence of ligand. An example of this monitoring, among other examples well-known and available to those in the art, was reported by Traynor and Nahorski in 1995. The preferred use of this assay system is for initial screening of candidate compounds because the

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system is generically applicable to all G protein-coupled receptors regardless of the particular G protein that interacts with the intracellular domain of the receptor.

2. Specific GPCR screening assay techniques

Once candidate compounds are identified using the "generic" G protein-coupled
5 receptor assay (*i.e.*, an assay to select compounds that are agonists, partial agonists, or inverse agonists), further screening to confirm that the compounds have interacted at the receptor site is preferred. For example, a compound identified by the "generic" assay may not bind to the receptor, but may instead merely "uncouple" the G protein from the intracellular domain.

a. *Gs, Gz and Gi.*

10 Gs stimulates the enzyme adenylyl cyclase. Gi (and Gz and Go), on the other hand, inhibit this enzyme. Adenylyl cyclase catalyzes the conversion of ATP to cAMP; thus, constitutively activated GPCRs that couple the Gs protein are associated with increased cellular levels of cAMP. On the other hand, constitutively activated GPCRs that couple Gi (or Gz, Go) protein are associated with decreased cellular levels of cAMP. *See, generally,*
15 "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols, J.G. et al eds. Sinauer Associates, Inc. (1992). Thus, assays that detect cAMP can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to the receptor (*i.e.*, such a compound would decrease the levels of cAMP). A variety of approaches known in the art for measuring cAMP can be utilized; a most preferred approach relies upon the use
20 of anti-cAMP antibodies in an ELISA-based format. Another type of assay that can be utilized is a whole cell second messenger reporter system assay. Promoters on genes drive the expression of the proteins that a particular gene encodes. Cyclic AMP drives gene expression by promoting the binding of a cAMP-responsive DNA binding protein or

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transcription factor (CREB) that then binds to the promoter at specific sites called cAMP response elements and drives the expression of the gene. Reporter systems can be constructed which have a promoter containing multiple cAMP response elements before the reporter gene, *e.g.*, β -galactosidase or luciferase. Thus, a constitutively activated Gs-linked receptor causes
5 the accumulation of cAMP that then activates the gene and expression of the reporter protein. The reporter protein such as β -galactosidase or luciferase can then be detected using standard biochemical assays (Chen et al. 1995).

b. Go and Gq.

10 Gq and Go are associated with activation of the enzyme phospholipase C, which in turn hydrolyzes the phospholipid PIP_2 , releasing two intracellular messengers: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). Increased accumulation of IP_3 is associated with activation of Gq- and Go-associated receptors. *See, generally*, "Indirect Mechanisms of Synaptic Transmission," Chpt. 8, From Neuron To Brain (3rd Ed.) Nichols,
15 J.G. et al eds. Sinauer Associates, Inc. (1992). Assays that detect IP_3 accumulation can be utilized to determine if a candidate compound is, *e.g.*, an inverse agonist to a Gq- or Go-associated receptor (*i.e.*, such a compound would decrease the levels of IP_3). Gq-associated receptors can also be examined using an AP1 reporter assay in that Gq-dependent phospholipase C causes activation of genes containing AP1 elements; thus, activated Gq-
20 associated receptors will evidence an increase in the expression of such genes, whereby inverse agonists thereto will evidence a decrease in such expression, and agonists will evidence an increase in such expression. Commercially available assays for such detection are available.

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3. GPCR Fusion Protein

The use of an endogenous, constitutively activate orphan GPCR or a non-endogenous, constitutively activated orphan GPCR, for use in screening of candidate compounds for the direct identification of inverse agonists, agonists and partial agonists provide an interesting
5 screening challenge in that, by definition, the receptor is active even in the absence of an endogenous ligand bound thereto. Thus, in order to differentiate between, *e.g.*, the non-endogenous receptor in the presence of a candidate compound and the non-endogenous receptor in the absence of that compound, with an aim of such a differentiation to allow for an understanding as to whether such compound may be an inverse agonist, agonist, partial
10 agonist or have no affect on such a receptor, it is preferred that an approach be utilized that can enhance such differentiation. A preferred approach is the use of a GPCR Fusion Protein.

Generally, once it is determined that a non-endogenous orphan GPCR has been constitutively activated using the assay techniques set forth above (as well as others), it is possible to determine the predominant G protein that couples with the endogenous GPCR.
15 Coupling of the G protein to the GPCR provides a signaling pathway that can be assessed. Because it is most preferred that screening take place by use of a mammalian expression system, such a system will be expected to have endogenous G protein therein. Thus, by definition, in such a system, the non-endogenous, constitutively activated orphan GPCR will continuously signal. In this regard, it is preferred that this signal be enhanced such that in the
20 presence of, *e.g.*, an inverse agonist to the receptor, it is more likely that it will be able to more readily differentiate, particularly in the context of screening, between the receptor when it is contacted with the inverse agonist.

The GPCR Fusion Protein is intended to enhance the efficacy of G protein coupling

- 20 -

with the non-endogenous GPCR. The GPCR Fusion Protein is preferred for screening with a non-endogenous, constitutively activated GPCR because such an approach increases the signal that is most preferably utilized in such screening techniques. This is important in facilitating a significant "signal to noise" ratio; such a significant ratio is import preferred for
5 the screening of candidate compounds as disclosed herein.

The construction of a construct useful for expression of a GPCR Fusion Protein is within the purview of those having ordinary skill in the art. Commercially available expression vectors and systems offer a variety of approaches that can fit the particular needs of an investigator. The criteria of importance for such a GPCR Fusion Protein construct is
10 that the endogenous GPCR sequence and the G protein sequence both be in-frame (preferably, the sequence for the endogenous GPCR is upstream of the G protein sequence) and that the "stop" codon of the GPCR must be deleted or replaced such that upon expression of the GPCR, the G protein can also be expressed. The GPCR can be linked directly to the G protein, or there can be spacer residues between the two (preferably, no more than about 12,
15 although this number can be readily ascertained by one of ordinary skill in the art). We have a preference (based upon convenience) of use of a spacer in that some restriction sites that are not used will, effectively, upon expression, become a spacer. Most preferably, the G protein that couples to the non-endogenous GPCR will have been identified prior to the creation of the GPCR Fusion Protein construct. Because there are only a few G proteins that have been
20 identified, it is preferred that a construct comprising the sequence of the G protein (*i.e.*, a universal G protein construct) be available for insertion of an endogenous GPCR sequence therein; this provides for efficiency in the context of large-scale screening of a variety of different endogenous GPCRs having different sequences.

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As noted above, constitutively activated GPCRs that couple to Gi, Gz and Go are expected to inhibit the formation of cAMP making assays based upon these types of GPCRs challenging (*i.e.*, the cAMP signal decreases upon activation thus making the direct identification of, *e.g.*, inverse agonists (which would further decrease this signal), interesting).

5 As will be disclosed herein, we have ascertained that for these types of receptors, it is possible to create a GPCR Fusion Protein that is not based upon the endogenous GPCR's endogenous G protein, in an effort to establish a viable cyclase-based assay. Thus, for example, a Gz coupled receptor such as H9, a GPCR Fusion Protein can be established that utilizes a Gs fusion protein – we believe that such a fusion construct, upon expression, "drives" or "forces"
10 the non-endogenous GPCR to couple with, *e.g.*, Gs rather than the "natural" Gz protein, such that a cyclase-based assay can be established. Thus, for Gi, Gz and Go coupled receptors, we prefer that that when a GPCR Fusion Protein is used and the assay is based upon detection of adenylyl cyclase activity, that the fusion construct be established with Gs (or an equivalent G protein that stimulates the formation of the enzyme adenylyl cyclase).

15 F. Medicinal Chemistry

Generally, but not always, direct identification of candidate compounds is preferably conducted in conjunction with compounds generated via combinatorial chemistry techniques, whereby thousands of compounds are randomly prepared for such analysis. Generally, the results of such screening will be compounds having unique core structures; thereafter, these
20 compounds are preferably subjected to additional chemical modification around a preferred core structure(s) to further enhance the medicinal properties thereof. Such techniques are known to those in the art and will not be addressed in detail in this patent document.

G. Pharmaceutical compositions

Candidate compounds selected for further development can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers are available to those in the art; for example, see
5 Remington's Pharmaceutical Sciences, 16th Edition, 1980, Mack Publishing Co., (Oslo et al., eds.)

H. Other Utility

Although a preferred use of the non-endogenous versions the human GPCRs disclosed herein may be for the direct identification of candidate compounds as inverse agonists,
10 agonists or partial agonists (preferably for use as pharmaceutical agents), these versions of human GPCRs can also be utilized in research settings. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, both normal and diseased, as well as understanding the role of constitutive activation as it applies to understanding the signaling
15 cascade. The value in non-endogenous human GPCRs is that their utility as a research tool is enhanced in that, because of their unique features, non-endogenous human GPCRs can be used to understand the role of these receptors in the human body before the endogenous ligand therefor is identified. Other uses of the disclosed receptors will become apparent to those in the art based upon, *inter alia*, a review of this patent document.

20

EXAMPLES

The following examples are presented for purposes of elucidation, and not limitation, of the present invention. While specific nucleic acid and amino acid sequences are disclosed herein, those of ordinary skill in the art are credited with the ability to make minor

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modifications to these sequences while achieving the same or substantially similar results reported below. The traditional approach to application or understanding of sequence cassettes from one sequence to another (*e.g.* from rat receptor to human receptor or from human receptor A to human receptor B) is generally predicated upon sequence alignment techniques whereby the sequences are aligned in an effort to determine areas of commonality. The mutational approach disclosed herein does not rely upon this approach but is instead based upon an algorithmic approach and a positional distance from a conserved proline residue located within the TM6 region of human GPCRs. Once this approach is secured, those in the art are credited with the ability to make minor modifications thereto to achieve substantially the same results (*i.e.*, constitutive activation) disclosed herein. Such modified approaches are considered within the purview of this disclosure

Example 1**ENDOGENOUS HUMAN GPCRS****1. Identification of Human GPCRs**

Certain of the disclosed endogenous human GPCRs were identified based upon a review of the GenBank™ database information. While searching the database, the following cDNA clones were identified as evidenced below (Table C).

TABLE C

| Disclosed Human Orphan GPCRs | Accession Number | Complete DNA Sequence (Base Pairs) | Open Reading Frame (Base Pairs) | Nucleic Acid SEQ.ID. NO. | Amino Acid SEQ.ID. NO. |
|------------------------------|------------------|------------------------------------|---------------------------------|--------------------------|------------------------|
| hARE-3 | AL033379 | 111,389 bp | 1,260 bp | 1 | 2 |
| hARE-4 | AC006087 | 226,925 bp | 1,119 bp | 3 | 4 |
| hARE-5 | AC006255 | 127,605 bp | 1,104 bp | 5 | 6 |
| hRUP3 | AL035423 | 140,094 bp | 1,005 bp | 7 | 8 |

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| | | | | | |
|-------|----------|------------|----------|----|----|
| hRUP5 | AC005849 | 169,144 bp | 1,413 bp | 9 | 10 |
| hRUP6 | AC005871 | 218,807 bp | 1,245 bp | 11 | 12 |
| hRUP7 | AC007922 | 158,858 bp | 1,173 bp | 13 | 14 |

Other disclosed endogenous human GPCRs were identified by conducting a BLAST™
 5 search of EST database (dbest) using the following EST clones as query sequences. The
 following EST clones identified were then used as a probe to screen a human genomic library
 (Table D).

TABLE D

| 10 | Disclosed Human Orphan GPCRs | Query (Sequence) | EST Clone/ Accession No. Identified | Open Reading Frame (Base Pairs) | Nucleic Acid SEQ.ID.NO. | Amino Acid SEQ.ID.NO. |
|----|---------------------------------------|--------------------------|---|--|----------------------------|--------------------------|
| | hGPCR27 | Mouse GPCR27 | AA775870 | 1,125 bp | 17 | 18 |
| | hARE-1 | TDAG | 1689643 AI090920 | 999 bp | 19 | 20 |
| 15 | hARE-2 | GPCR27 | 68530 AA359504 | 1,122 bp | 21 | 22 |
| | hPPR1 | Bovine PPR1 | 238667 H67224 | 1,053 bp | 23 | 24 |
| | hG2A | Mouse 1179426 | <i>See Example 2(a), below</i> | 1,113 bp | 25 | 26 |
| | hCHN3 | N.A. | EST 36581 (full length) | 1,113 bp | 27 | 28 |
| | hCHN4 | TDAG | 1184934 AA804531 | 1,077 bp | 29 | 30 |
| 20 | hCHN6 | N.A. | EST 2134670 (full length) | 1,503 bp | 31 | 32 |
| | hCHN8 | KIAA0001 | EST 764455 | 1,029 bp | 33 | 34 |
| | hCHN 9 | 1365839 | EST 1541536 | 1,077 bp | 35 | 36 |
| | hCHN10 | Mouse EST 1365839 | Human 1365839 | 1,005 bp | 37 | 38 |
| | hRUP4 | N.A. | AI307658 | 1,296 bp | 39 | 40 |
| 25 | | N.A. = "not applicable". | | | | |

2. Full Length Cloning

a. Human G2A

Mouse EST clone 1179426 was used to obtain a human genomic clone containing all

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but three amino acid G2A coding sequences. The 5' of this coding sequence was obtained by using 5'RACE, and the template for PCR was Clontech's Human Spleen Marathon-Ready™ cDNA. The disclosed human G2A was amplified by PCR using the G2A cDNA specific primers for the first and second round PCR as shown in SEQ.ID.NO.: 41 and SEQ.ID.NO.:42

5 as follows:

5'-CTGTGTACAGCAGTTCGCAGAGTG-3' (SEQ.ID.NO.: 41; 1st round PCR)

5'-GAGTGCCAGGCAGAGCAGGTAGAC-3' (SEQ.ID.NO.: 42; second round PCR).

PCR was performed using Advantage GC Polymerase Kit (Clontech; manufacturing instructions will be followed), at 94°C for 30 sec followed by 5 cycles of 94°C for 5 sec and
10 72°C for 4 min; and 30 cycles of 94° for 5 sec and 70° for 4 min. An approximate 1.3 Kb PCR fragment was purified from agarose gel, digested with Hind III and Xba I and cloned into the expression vector pRC/CMV2 (Invitrogen). The cloned-insert was sequenced using the T7 Sequenase™ kit (USB Amersham; manufacturer instructions followed) and the sequence was compared with the presented sequence. Expression of the human G2A was detected by
15 probing an RNA dot blot (Clontech; manufacturer instructions followed) with the P³²-labeled fragment.

b. CHN9

Sequencing of the EST clone 1541536 showed CHN9 to be a partial cDNA clone having only an initiation codon; *i.e.*, the termination codon was missing. When CHN9
20 was used to blast against data base (nr), the 3' sequence of CHN9 was 100% homologous to the 5' untranslated region of the leukotriene B4 receptor cDNA, which contained a termination codon in the frame with CHN9 coding sequence. To determine whether the 5' untranslated region of LTB4R cDNA was the 3' sequence of CHN9, PCR was performed using primers based upon the 5' sequence flanking the initiation codon found in CHN9 and

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the 3' sequence around the termination codon found in the LTB4R 5' untranslated region.

The 5' primer sequence utilized was as follows:

5'-CCCGAATTCCTGCTTGCTCCCAGCTTGGCCC-3' (SEQ.ID.NO.: 43; sense) and

5'-TGTGGATCCTGCTGTCAAAGGTCCCATTCCGG-3' (SEQ.ID.NO.: 44; antisense).

- 5 PCR was performed using thymus cDNA as a template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 65°C for 1min and 72 °C for 1 min and 10 sec. A 1.1kb fragment consistent with the predicted size was obtained from PCR. This PCR fragment was subcloned into pCMV (*see* below) and
- 10 sequenced (*see*, SEQ.ID.NO.: 35).

c. RUP 4

The full length RUP4 was cloned by RT-PCR with human brain cDNA (Clontech) as templates:

5'-TCACAATGCTAGGTGTGGTC-3' (SEQ.ID.NO.: 45; sense) and

- 15 5'-TGCATAGACAATGGGATTACAG-3' (SEQ.ID.NO.: 46; antisense).

PCR was performed using TaqPlus Precision™ polymerase (Stratagene; manufacturing instructions followed) by the following cycles: 94°C for 2 min; 94°C 30 sec; 55°C for 30 sec, 72°C for 45 sec, and 72°C for 10 min. Cycles 2 through 4 were repeated 30 times.

- The PCR products were separated on a 1% agarose gel and a 500 bp PCR fragment
- 20 was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the T7 DNA Sequenase™ kit (Amsham) and the SP6/T7 primers (Stratagene). Sequence analysis revealed that the PCR fragment was indeed an alternatively spliced form of AI307658 having a continuous open reading frame with similarity to other GPCRs. The completed sequence of this PCR fragment was as follows:

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5'-TCACAATGCTAGGTGTGGTCTGGCTGGTGGCAGTCATCGTAGGATCACCCATGTGGCAC
 GTGCAACAACCTTGAGATCAAATATGACTTCCTATATGAAAAGGAACACATCTGCTGCTTAAGA
 GTGGACCAGCCCTGTGCACCAGAAGATCTACACCACCTTCATCCTTGTCATCCTCTTCCTCCTGC
 CTCTTATGGTGATGCTTATTCTGTACGTAAAATTGGTTATGAACCTTTGGATAAAGAAAAGAGTT
 5 GGGGATGGTTCAGTGCTTCGAACTATTCATGGAAAAGAAATGTCCAAAATAGCCAGGAAGAAG
 AAACGAGCTGTCATTATGATGGTGACAGTGGTGGCTCTCTTTGCTGTGTGCTGGGCACCATTC
 ATGTTGTCCATATGATGATTGAATACAGTAATTTTGAAGAAGGAATATGATGATGTCACAATCAA
 GATGATTTTTGCTATCGTGCAAATTATTGGATTTTCCAACCTCCATCTGTAATCCCATTGTCTATGCA-
 3' (SEQ.ID.NO.: 47)

10 Based on the above sequence, two sense oligonucleotide primer sets:

5'-CTGCTTAGAAGAGTGGACCAG-3' (SEQ.ID.NO.: 48; oligo 1),

5'-CTGTGCACCAGAAGATCTACAC-3' (SEQ.ID.NO.: 49; oligo 2) and

two antisense oligonucleotide primer sets:

5'-CAAGGATGAAGGTGGTGTAGA-3' (SEQ.ID.NO.: 50; oligo 3)

15 5'-GTGTAGATCTTCTGGTGCACAGG-3' (SEQ.ID.NO.: 51; oligo 4)

were used for 3'- and 5'-RACE PCR with a human brain Marathon-Ready™ cDNA (Clontech, Cat# 7400-1) as template, according to manufacture's instructions. DNA fragments generated by the RACE PCR were cloned into the pCRII-TOPO™ vector (Invitrogen) and sequenced using the SP6/T7 primers (Stratagene) and some internal primers.

20 The 3' RACE product contained a poly(A) tail and a completed open reading frame ending at a TAA stop codon. The 5' RACE product contained an incomplete 5' end; *i.e.*, the ATG initiation codon was not present.

Based on the new 5' sequence, oligo 3 and the following primer:

5'-GCAATGCAGGTCATAGTGAGC-3' (SEQ.ID.NO.: 52; oligo 5)

25 were used for the second round of 5' race PCR and the PCR products were analyzed as above.

A third round of 5' race PCR was carried out utilizing antisense primers:

5'-TGGAGCATGGTGACGGGAATGCAGAAG-3' (SEQ.ID.NO.: 53; oligo 6) and

5'-GTGATGAGCAGGTCACTGAGCGCCAAG-3' (SEQ.ID.NO.: 54; oligo 7).

The sequence of the 5' RACE PCR products revealed the presence of the initiation codon

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ATG, and further round of 5' race PCR did not generate any more 5' sequence. The completed 5' sequence was confirmed by RT-PCR using sense primer

5'-GCAATGCAGGCGCTTAACATTAC-3' (SEQ.ID.NO.: 55; oligo 8)

and oligo 4 as primers and sequence analysis of the 650 bp PCR product generated from

5 human brain and heart cDNA templates (Clontech, Cat# 7404-1). The completed 3' sequence was confirmed by RT-PCR using oligo 2 and the following antisense primer:

5'-TTGGGTTACAATCTGAAGGGCA-3' (SEQ.ID.NO.:56; oligo 9)

and sequence analysis of the 670 bp PCR product generated from human brain and heart cDNA templates. (Clontech, Cat# 7404-1).

10 d. RUP5

The full length RUP5 was cloned by RT-PCR using a sense primer upstream from ATG, the initiation codon (SEQ.ID.NO.:57), and an antisense primer containing TCA as the stop codon (SEQ.ID.NO.:58), which had the following sequences:

5'-ACTCCGTGTCCAGCAGGACTCTG-3' (SEQ.ID.NO.: 57)

15 5'-TGC GTG TTCCTGGACCCTCACGTG-3' (SEQ.ID.NO.: 58)

and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50ul reaction by the following cycle with step 2 through step 4 repeated 30 times: 94°C for 30 sec; 94° for 15 sec; 69° for 40 sec; 72°C for 3 min; and 72°C fro 6 min. A 1.4kb PCR fragment was isolated and cloned with
20 the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the T7 DNA Sequenase™ kit (Amsham). See, SEQ.ID.NO.: 9.

e. RUP6

The full length RUP6 was cloned by RT-PCR using primers:

5'-CAGGCCTTGGATTTTAATGTCAGGGATGG-3' (SEQ.ID.NO.: 59) and

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5'-GGAGAGTCAGCTCTGAAAGAATTCAGG-3' (SEQ.ID.NO.: 60);
and human thymus Marathon-Ready™ cDNA (Clontech) as a template. Advantage cDNA polymerase (Clontech, according to manufacturer's instructions) was used for the amplification in a 50ul reaction by the following cycle: 94°C for 30sec; 94°C for 5 sec; 66°C
5 for 40sec; 72°C for 2.5 sec and 72°C for 7 min. Cycles 2 through 4 were repeated 30 times. A 1.3 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced (*see*, SEQ.ID.NO.: 11) using the ABI Big Dye Terminator™ kit (P.E. Biosystem).

f. RUP7

10 The full length RUP7 was cloned by RT-PCR using primers:
5'-TGATGTGATGCCAGATACTAATAGCAC-3' (SEQ.ID.NO.: 61; sense) and
5'-CCTGATTCATTTAGGTGAGATTGAGAC-3' (SEQ.ID.NO.: 62; antisense)
and human peripheral leukocyte cDNA (Clontech) as a template. Advantage™ cDNA polymerase (Clontech) was used for the amplification in a 50 ul reaction by the following
15 cycle with step 2 to step 4 repeated 30 times: 94°C for 2 minutes; 94°C for 15 seconds; 60°C for 20 seconds; 72°C for 2 minutes; 72°C for 10 minutes. A 1.25 Kb PCR fragment was isolated and cloned into the pCRII-TOPO™ vector (Invitrogen) and completely sequenced using the ABI Big Dye Terminator™ kit (P.E. Biosystem). *See*, SEQ.ID.NO.: 13.

3. Angiotensin II Type 1 Receptor ("AT1")

20 The endogenous human angiotensin II type 1 receptor ("AT1") was obtained by PCR using genomic DNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 µM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min. The 5' PCR primer contains a HindIII site with the sequence:

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5'-CCCAAGCTTCCCCAGGTGTTATTTGAT-3' (SEQ.ID.NO.: 63)

and the 3' primer contains a BamHI site with the following sequence:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 64).

The resulting 1.3 kb PCR fragment was digested with HindIII and BamHI and cloned into
5 HindIII-BamHI site of pCMV expression vector. The cDNA clone was fully sequenced.
Nucleic acid (SEQ.ID.NO.: 65) and amino acid (SEQ.ID.NO.: 66) sequences for human AT1
were thereafter determined and verified.

4. GPR38

To obtain GPR38, PCR was performed by combining two PCR fragments, using
10 human genomic cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system
provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides.
The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 62°C for 1min
and 72°C for 2 min.

The first fragment was amplified with the 5' PCR primer that contained an end site
15 with the following sequence:

5'-ACCATGGGCAGCCCCTGGAACGGCAGC-3' (SEQ.ID.NO.:67)

and a 3' primer having the following sequence:

5'-AGAACCACCACCAGCAGGACGCGGACGGTCTGCCGGTGG-3' (SEQ.ID.NO.:68).

The second PCR fragment was amplified with a 5' primer having the following sequence:

20 5'-GTCCGCGTCCTGCTGGTGGTGGTTCTGGCATTATAATT-3' (SEQ.ID.NO.: 69)

and a 3' primer that contained a BamHI site and having the following sequence:

5'-CCTGGATCCTTATCCCATCGTCTTCACGTTAGC-3' (SEQ.ID.NO.: 70).

The two fragments were used as templates to amplify GPR38, using SEQ.ID.NO.: 67 and
SEQ.ID.NO.: 70 as primers (using the above-noted cycle conditions). The resulting 1.44kb

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PCR fragment was digested with BamHI and cloned into Blunt-BamHI site of pCMV expression vector.

5. MC4

To obtain MC4, PCR was performed using human genomic cDNA as template and
5 rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 54°C for 1min and 72°C for 1.5 min.

The 5' PCR contained an EcoRI site with the sequence:

5'-CTGGAATTCTCCTGCCAGCATGGTGA-3' (SEQ.ID.NO.: 71)

10 and the 3' primer contained a BamHI site with the sequence:

5'-GCAGGATCCTATATTGCGTGCTCTGTCCCC'-3 (SEQ.ID.NO.: 72).

The 1.0 kb PCR fragment was digest with EcoRI and BamHI and cloned into EcoRI-BamHI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 73) and amino acid (SEQ.ID.NO.: 74) sequences for human MC4 were thereafter determined.

15 6. CCKB

To obtain CCKB, PCR was performed using human stomach cDNA as template and rTth polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25uM of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition for each PCR reaction was 30 cycles of 94°C for 1 min, 65°C for 1min and 72°C for 1 min and 30 sec.

20 The 5' PCR contained a HindIII site with the sequence:

5'-CCGAAGCTTCGAGCTGAGTAAGGCGGCGGGCT-3' (SEQ.ID.NO.: 75)

and the 3' primer contained an EcoRI site with the sequence:

5'-GTGGAATTCATTTGCCCTGCCTCAACCCCCA-3 (SEQ.ID.NO.: 76).

The resulting 1.44 kb PCR fragment was digest with HindIII and EcoRI and cloned into

HindIII-EcoRI site of pCMV expression vector. Nucleic acid (SEQ.ID.NO.: 77) and amino acid (SEQ.ID.NO.: 78) sequences for human CCKB were thereafter determined.

7. TDAG8

To obtain TDAG8, PCR was performed using genomic DNA as template and rTth
5 polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 56°C for 1min and 72 °C for 1 min and 20 sec. The 5' PCR primer contained a HindIII site with the following sequence:

5'-TGCAAGCTTAAAAAGGAAAAAATGAACAGC-3' (SEQ.ID.NO.: 79)

10 and the 3' primer contained a BamHI site with the following sequence:

5'-TAAGGATCCCTTCCCTTCAAAACATCCTTG -3' (SEQ.ID.NO.: 80).

The resulting 1.1 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. Three resulting clones sequenced contained three potential polymorphisms involving changes of amino acid 43 from Pro to Ala, amino
15 acid 97 from Lys to Asn and amino acid 130 from Ile to Phe. Nucleic acid (SEQ.ID.NO.: 81) and amino acid (SEQ.ID.NO.: 82) sequences for human TDAG8 were thereafter determined.

8. H9

To obtain H9, PCR was performed using pituitary cDNA as template and rTth
20 polymerase (Perkin Elmer) with the buffer system provided by the manufacturer, 0.25 μ M of each primer, and 0.2 mM of each 4 nucleotides. The cycle condition was 30 cycles of 94°C for 1 min, 62°C for 1 min and 72°C for 2 min. The 5' PCR primer contained a HindIII site with the following sequence:

5'-GGAAAGCTTAACGATCCCCAGGAGCAACAT-3' (SEQ.ID.NO.:15)

and the 3' primer contained a BamHI site with the following sequence:

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5'-CTGGGATCCTACGAGAGCATTTTTTCACACAG-3' (SEQ.ID.NO.:16).

The resulting 1.9 kb PCR fragment was digested with HindIII and BamHI and cloned into HindIII-BamHI site of pCMV expression vector. H9 contained three potential polymorphisms involving changes of amino acid P320S, S493N and amino acid G448A. Nucleic acid
5 (SEQ.ID.NO.: 139) and amino acid (SEQ.ID.NO.: 140) sequences for human H9 were thereafter determined and verified.

Example 2

PREPARATION OF NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED GPCRS

Those skilled in the art are credited with the ability to select techniques for
10 mutation of a nucleic acid sequence. Presented below are approaches utilized to create non-endogenous versions of several of the human GPCRs disclosed above. The mutations disclosed below are based upon an algorithmic approach whereby the 16th amino acid (located in the IC3 region of the GPCR) from a conserved proline residue (located in the TM6 region of the GPCR, near the TM6/IC3 interface) is mutated, most preferably to a
15 lysine amino acid residue.

1. Transformer Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs may be accomplished on human GPCRs using Transformer Site-Directed™ Mutagenesis Kit (Clontech) according to the manufacturer instructions. Two mutagenesis primers are utilized, most preferably a lysine
20 mutagenesis oligonucleotide that creates the lysine mutation, and a selection marker oligonucleotide. For convenience, the codon mutation to be incorporated into the human GPCR is also noted, in standard form (Table E):

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TABLE E

| | Receptor Identifier | Codon Mutation |
|----|---------------------|----------------|
| | hARE-3 | F313K |
| | hARE-4 | V233K |
| 5 | hARE-5 | A240K |
| | hGPCR14 | L257K |
| | hGPCR27 | C283K |
| | hARE-1 | E232K |
| | hARE-2 | G285K |
| 10 | hPPR1 | L239K |
| | hG2A | K232A |
| | hRUP3 | L224K |
| | hRUP5 | A236K |
| | hRUP6 | N267K |
| 15 | hRUP7 | A302K |
| | hCHN4 | V236K |
| | hMC4 | A244K |
| | hCHN3 | S284K |
| | hCHN6 | L352K |
| 20 | hCHN8 | N235K |
| | hCHN9 | G223K |
| | hCHN10 | L231K |
| | hH9 | F236K |

The following GPCRs were mutated according with the above method using the

25 designated sequence primers (Table F).

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TABLE F

| Receptor Identifier | Codon Mutation | Lysine Mutagenesis (SEQ.ID.NO.) 5'-3' orientation, mutation sequence underlined | Selection Marker (SEQ.ID.NO.) 5'-3' orientation |
|---------------------|------------------|--|---|
| hRUP4 | V272K | CAGGAAGAAG <u>AAA</u> CGAGC TGTCATTATGATGGTGACA GTG (83) | CACTGTCACCATCATAATG ACAGCTCGTTTCTTCTTCC TG (84) |
| hAT1 | <i>see below</i> | alternative approach; <i>see below</i> | alternative approach; <i>see below</i> |
| hGPR38 | V297K | GGCCACCGGCAGACCA <u>AAAC</u> GCGTCCTGCTG (85) | CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (86) |
| hCCKB | V332K | alternative approach; <i>see below</i> | alternative approach; <i>see below</i> |
| hTDAG8 | I225K | GGAAAAGAAGAGAATCAA <u>AAA</u> ACTACTTGTCAGCATC (87) | CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (88) |
| hH9 | F236K | GCTGAGGTTTCGCAATA <u>AAAC</u> TAACCATGTTTGTG (143) | CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (144) |
| hMC4 | A244K | GCCAATATGAAGGGAA <u>AAA</u> ATTACCTTGACCATC (137) | CTCCTTCGGTCCTCCTATC GTTGTCAGAAGT (138) |

The non-endogenous human GPCRs were then sequenced and the derived and verified nucleic acid and amino acid sequences are listed in the accompanying "Sequence Listing" appendix to this patent document, as summarized in Table G below:

TABLE G

| | Non Endogenous Human GPCR | Nucleic Acid Sequence Listing | Amino Acid Sequence Listing |
|----|---|---|---|
| 15 | hRUP4 (V272K) | SEQ.ID.NO.: 127 | SEQ.ID.NO.: 128 |
| 20 | hAT1 (<i>see alternative approaches below</i>) | (<i>see alternative approaches below</i>) | (<i>see alternative approaches below</i>) |
| | hGPR38 (V297K) | SEQ.ID.NO.: 129 | SEQ.ID.NO.: 130 |
| 25 | hCCKB (V332K) | SEQ.ID.NO.: 131 | SEQ.ID.NO.: 132 |
| | hTDAG8 (I225K) | SEQ.ID.NO.: 133 | SEQ.ID.NO.: 134 |
| | hH9 (F236K) | SEQ.ID.NO.: 141 | SEQ.ID.NO.: 142 |
| 30 | hMC4 (A244K) | SEQ.ID.NO.: 135 | SEQ.ID.NO.: 136 |

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2. Alternative Approaches For Creation of Non-Endogenous Human GPCRs

a. AT1

1. F239K Mutation

Preparation of a non-endogenous, constitutively activated human AT1 receptor was accomplished by creating an F239K mutation (see, SEQ.ID.NO.: 89 for nucleic acid sequence, and SEQ.ID.NO.: 90 for amino acid sequence). Mutagenesis was performed using Transformer Site-Directed Mutagenesis™ Kit (Clontech) according to the to manufacturer's instructions. The two mutagenesis primers were used, a lysine mutagenesis oligonucleotide (SEQ.ID.NO.: 91) and a selection marker oligonucleotide (SEQ.ID.NO.: 92), which had the following sequences:

5'-CCAAGAAATGATGATATTAAAAAGATAATTATGGC-3' (SEQ.ID.NO.: 91)

5'-CTCCTTCGGTCCTCCTATCGTTGTCAGAAGT-3' (SEQ.ID.NO.: 92),

respectively.

2. N111A Mutation

Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an N111A mutation (see, SEQ.ID.NO.:93 for nucleic acid sequence, and SEQ.ID.NO.: 94 for amino acid sequence). Two PCR reactions were performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer, supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer used had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 95)

and the antisense primer had the following sequence:

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5'-CCTGCAGGCGAAACTGACTCTGGCTGAAG-3' (SEQ.ID.NO.: 96).

The resulting 400 bp PCR fragment was digested with HindIII site and subcloned into HindIII-SmaI site of pCMV vector (5' construct). The 3' PCR sense primer used had the following sequence:

5 5'-CTGTACGCTAGTGTGTTTCTACTCACGTGTCTCAGCATTGAT-3' (SEQ.ID.NO.: 97)

and the antisense primer had the following sequence:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 98)

The resulting 880 bp PCR fragment was digested with BamHI and inserted into Pst (blunted by T4 polymerase) and BamHI site of 5' construct to generated the full length
10 N111A construct. The cycle condition was 25 cycles of 94°C for 1 min, 60°C for 1min and 72 °C for 1 min (5' PCR) or 1.5 min (3' PCR).

3. AT2K255IC3 Mutation

Preparation of a non-endogenous, constitutively activated human AT1 was accomplished by creating an AT2K255IC3 "domain swap" mutation (see, SEQ.ID.NO.:99
15 for nucleic acid sequence, and SEQ.ID.NO.: 100 for amino acid sequence). Restriction sites flanking IC3 of AT1 were generated to facilitate replacement of the IC3 with corresponding IC3 from angiotensin II type 2 receptor (AT2). This was accomplished by performing two PCR reactions. A 5' PCR fragment (Fragment A) encoded from the 5' untranslated region to the beginning of IC3 was generated by utilizing SEQ.ID.NO.: 63 as
20 sense primer and the following sequence:

5'-TCCGAATTCCAAAATAACTTGTAAGAATGATCAGAAA-3' (SEQ.ID.NO.: 101)

as antisense primer. A 3' PCR fragment (Fragment B) encoding from the end of IC3 to the 3' untranslated region was generated by using the following sequence:

5'-AGATCTTAAGAAGATAATTATGGCAATTGTGCT-3' (SEQ.ID.NO.: 102)

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as sense primer and SEQ.ID.NO.: 64 as antisense primer. The PCR condition was 30 cycles of 94°C for 1 min, 55°C for 1min and 72°C for 1.5 min using endogenous AT1 cDNA clone as template and pfu polymerase (Stratagene), with the buffer systems provided by the manufacturer, supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. Fragment A (720 bp) was digested with HindIII and EcoRI and subcloned. Fragment B was digested with BamHI and subcloned into pCMV vector with an EcoRI site 5' to the cloned PCR fragment.

The DNA fragment (Fragment C) encoding IC3 of AT2 with a L255K mutation and containing an EcoRI cohesive end at 5' and a AflII cohesive end at 3', was generated by annealing 2 synthetic oligonucleotides having the following sequences:

5'AATTCGAAAACACTTACTGAAGACGAATAGCTATGGGAAGAACAGGATAACCCGTGACCAAG-3' (sense; SEQ.ID.NO.: 103)
5'TTAACTTGGTCACGGGTTATCCTGTTCTTCCCATAGCTATTCGTCTTCAGT
AAGTGTITTCG-3' (antisense; SEQ.ID.NO.: 104).

Fragment C was inserted in front of Fragment B through EcoRI and AflII site. The resulting clone was then ligated with the Fragment A through the EcoRI site to generate AT1 with AT2K255IC3.

4. A243+ Mutation

Preparation of a non-endogenous human AT1 receptor was also accomplished by creating an A243+ mutation (see, SEQ.ID.NO.: 105 for nucleic acid sequence, and SEQ.ID.NO.: 106 for amino acid sequence). An A243+ mutation was constructed using the following PCR based strategy: Two PCR reactions was performed using pfu polymerase (Stratagene) with the buffer system provided by the manufacturer supplemented with 10% DMSO, 0.25 µM of each primer, and 0.5 mM of each 4 nucleotides. The 5' PCR sense primer

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utilized had the following sequence:

5'-CCCAAGCTTCCCCAGGTGTATTTGAT-3' (SEQ.ID.NO.: 107)

and the antisense primer had the following sequence:

5'-AAGCACAATTGCTGCATAATTATCTTAAAAATATCATC-3' (SEQ.ID.NO.: 108).

- 5 The 3' PCR sense primer utilized had the following sequence:

5'-AAGATAATTATGGCAGCAATTGTGCTTTTCTTTTCTTT-3' (SEQ.ID.NO.: 109)

containing the Ala insertion and antisense primer:

5'-GTTGGATCCACATAATGCATTTTCTC-3' (SEQ.ID.NO.: 110).

The cycle condition was 25 cycles of 94°C for 1 min, 54°C for 1min and 72°C for 1.5 min.

- 10 An aliquot of the 5' and 3' PCR were then used as co-template to perform secondary PCR using the 5' PCR sense primer and 3' PCR antisense primer. The PCR condition was the same as primary PCR except the extension time was 2.5 min. The resulting PCR fragment was digested with HindIII and BamHI and subcloned into pCMV vector. (See, SEQ.ID.NO.: 105)

15 **4. CCKB**

Preparation of the non-endogenous, constitutively activated human CCKB receptor was accomplished by creating a V322K mutation (see, SEQ.ID.NO.: 111 for nucleic acid sequence and SEQ.ID.NO.: 112 for amino acid sequence). Mutagenesis was performed by PCR via amplification using the wildtype CCKB from Example 1.

- 20 The first PCR fragment (1kb) was amplified by using SEQ.ID.NO.: 75 and an antisense primer comprising a V322K mutation:

5'-CAGCAGCATGCGCTTCACGCGCTTCTTAGCCCAG-3' (SEQ.ID.NO.: 113).

The second PCR fragment (0.44kb) was amplified by using a sense primer comprising the V322K mutation:

5'-AGAAGCGCGTGAAGCGCATGCTGCTGGTGATCGTT-3' (SEQ.ID.NO.: 114) and SEQ.ID.NO.:

76.

The two resulting PCR fragments were then used as template for amplifying CCKB comprising V332K, using SEQ.ID.NO.: 75 and SEQ.ID.NO.: 76 and the above-noted
5 system and conditions. The resulting 1.44kb PCR fragment containing the V332K mutation was digested with HindIII and EcoRI and cloned into HindIII-EcoRI site of pCMV expression vector. (See, SEQ.ID.NO.: 111).

3. QuikChange™ Site-Directed™ Mutagenesis

Preparation of non-endogenous human GPCRs can also be accomplished by using
10 QuikChange™ Site-Directed™ Mutagenesis Kit (Stratagene, according to manufacturer's instructions). Endogenous GPCR is preferably used as a template and two mutagenesis primers utilized, as well as, most preferably, a lysine mutagenesis oligonucleotide and a selection marker oligonucleotide (included in kit). For convenience, the codon mutation incorporated into the human GPCR and the respective oligonucleotides are noted, in standard
15 form (Table H):

TABLE H

| Receptor Identifier | Codon Mutation | Lysine Mutagenesis (SEQ.ID.NO.) 5'-3' orientation, mutation underlined | Selection Marker (SEQ.ID.NO.) 5'-3' orientation |
|---------------------|----------------|---|--|
| hCHN3 | S284K | ATGGAGAAAAGAATCAA <u>AA</u> AGAA TGTTCTATATA (115) | TATATAGAACATTCTTTT GATTCTTTTCTCCAT (116) |
| hCHN6 | L352K | CGCTCTCTGGCCTTGA <u>AG</u> CGCAC GCTCAGC (117) | GCTGAGCGTGCGCTTCA AGGCCAGAGAGCG (118) |
| 5 hCHN8 | N235K | CCCAGGAAAAAGGTGA <u>AA</u> AGTCA AAGTTTTC (119) | GAAAACTTTGACTTTTCA CTTTTCTCTGGG (120) |
| hCHN9 | G223K | GGGGCGCGGGTGAA <u>AC</u> CGGCTGG TGAGC (121) | GCTCACCAGCCGTTTCA CCCGCGCCCC (122) |
| hCHN10 | L231K | CCCCTTGAA <u>AA</u> GCCTAAGAACTT GGTCATC (123) | GATGACCAAGTTCTTAG GCTTTTCAAGGGG (124) |

Example 3

RECEPTOR EXPRESSION

10 Although a variety of cells are available to the art for the expression of proteins, it is most preferred that mammalian cells be utilized. The primary reason for this is predicated upon practicalities, *i.e.*, utilization of, *e.g.*, yeast cells for the expression of a GPCR, while possible, introduces into the protocol a non-mammalian cell which may not (indeed, in the case of yeast, does not) include the receptor-coupling, genetic-mechanism and secretory

15 pathways that have evolved for mammalian systems – thus, results obtained in non-mammalian cells, while of potential use, are not as preferred as that obtained from mammalian cells. Of the mammalian cells, COS-7, 293 and 293T cells are particularly preferred, although the specific mammalian cell utilized can be predicated upon the particular needs of the artisan.

On day one, 1×10^7 293T cells per 150mm plate were plated out. On day two, two

20 reaction tubes were prepared (the proportions to follow for each tube are per plate): tube A was prepared by mixing 20 μ g DNA (*e.g.*, pCMV vector; pCMV vector with receptor cDNA, etc.) in 1.2ml serum free DMEM (Irvine Scientific, Irvine, CA); tube B was

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prepared by mixing 120 μ l lipofectamine (Gibco BRL) in 1.2ml serum free DMEM. Tubes A and B were admixed by inversions (several times), followed by incubation at room temperature for 30-45min. The admixture is referred to as the "transfection mixture".

Plated 293T cells were washed with 1XPBS, followed by addition of 10ml serum free DMEM. 2.4ml of the transfection mixture were added to the cells, followed by incubation for 4hrs at 37°C/5% CO₂. The transfection mixture was removed by aspiration, followed by the addition of 25ml of DMEM/10% Fetal Bovine Serum. Cells were incubated at 37°C/5% CO₂. After 72hr incubation, cells were harvested and utilized for analysis.

Example 4

10 ASSAYS FOR DETERMINATION OF CONSTITUTIVE ACTIVITY OF NON-ENDOGENOUS GPCRS

A variety of approaches are available for assessment of constitutive activity of the non-endogenous human GPCRs. The following are illustrative; those of ordinary skill in the art are credited with the ability to determine those techniques that are preferentially beneficial for the needs of the artisan.

1. Membrane Binding Assays: [³⁵S]GTP γ S Assay

When a G protein-coupled receptor is in its active state, either as a result of ligand binding or constitutive activation, the receptor couples to a G protein and stimulates the release of GDP and subsequent binding of GTP to the G protein. The alpha subunit of the G protein-receptor complex acts as a GTPase and slowly hydrolyzes the GTP to GDP, at which point the receptor normally is deactivated. Constitutively activated receptors continue to exchange GDP for GTP. The non-hydrolyzable GTP analog, [³⁵S]GTP γ S, can be utilized to demonstrate enhanced binding of [³⁵S]GTP γ S to membranes expressing constitutively activated receptors. The advantage of using [³⁵S]GTP γ S binding to measure constitutive

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activation is that: (a) it is generically applicable to all G protein-coupled receptors; (b) it is proximal at the membrane surface making it less likely to pick-up molecules which affect the intracellular cascade.

The assay utilizes the ability of G protein coupled receptors to stimulate [³⁵S]GTPγS
5 binding to membranes expressing the relevant receptors. The assay can, therefore, be used in the direct identification method to screen candidate compounds to known, orphan and constitutively activated G protein-coupled receptors. The assay is generic and has application to drug discovery at all G protein-coupled receptors.

The [³⁵S]GTPγS assay can be incubated in 20 mM HEPES and between 1 and about
10 20mM MgCl₂ (this amount can be adjusted for optimization of results, although 20mM is preferred) pH 7.4, binding buffer with between about 0.3 and about 1.2 nM [³⁵S]GTPγS (this amount can be adjusted for optimization of results, although 1.2 is preferred) and 12.5 to 75 μg membrane protein (*e.g.* COS-7 cells expressing the receptor; this amount can be adjusted for optimization, although 75μg is preferred) and 1 μM GDP (this amount can be changed for
15 optimization) for 1 hour. Wheatgerm agglutinin beads (25 μl; Amersham) should then be added and the mixture incubated for another 30 minutes at room temperature. The tubes are then centrifuged at 1500 x g for 5 minutes at room temperature and then counted in a scintillation counter.

A less costly but equally applicable alternative has been identified which also meets
20 the needs of large scale screening. Flash plates™ and Wallac™ scintistrips may be utilized to format a high throughput [³⁵S]GTPγS binding assay. Furthermore, using this technique, the assay can be utilized for known GPCRs to simultaneously monitor tritiated ligand binding to the receptor at the same time as monitoring the efficacy via [³⁵S]GTPγS binding. This is

possible because the Wallac beta counter can switch energy windows to look at both tritium and ^{35}S -labeled probes. This assay may also be used to detect other types of membrane activation events resulting in receptor activation. For example, the assay may be used to monitor ^{32}P phosphorylation of a variety of receptors (both G protein coupled and tyrosine kinase receptors). When the membranes are centrifuged to the bottom of the well, the bound ^{35}S GTP γ S or the ^{32}P -phosphorylated receptor will activate the scintillant which is coated of the wells. Scinti[®] strips (Wallac) have been used to demonstrate this principle. In addition, the assay also has utility for measuring ligand binding to receptors using radioactively labeled ligands. In a similar manner, when the radiolabeled bound ligand is centrifuged to the bottom of the well, the scintistrip label comes into proximity with the radiolabeled ligand resulting in activation and detection.

2. Adenylyl Cyclase

A Flash Plate[™] Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) designed for cell-based assays can be modified for use with crude plasma membranes. The Flash Plate wells contain a scintillant coating which also contains a specific antibody recognizing cAMP. The cAMP generated in the wells was quantitated by a direct competition for binding of radioactive cAMP tracer to the cAMP antibody. The following serves as a brief protocol for the measurement of changes in cAMP levels in membranes that express the receptors.

Transfected cells are harvested approximately three days after transfection. Membranes were prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl_2 . Homogenization is performed on ice using a Brinkman Polytron[™] for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000

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X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of measurement, the membrane pellet is slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl₂ (these amounts can be optimized, although the values listed herein are preferred), to yield a final protein concentration of 0.60mg/ml (the resuspended membranes were placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μ Ci of tracer [¹²⁵I] cAMP (100 μ l] to 11 ml Detection Buffer) are prepared and maintained in accordance with the manufacturer's instructions. Assay Buffer is prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM MgCl₂, 20mM (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μ M GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized. The assay is initiated by addition of 50ul of assay buffer followed by addition of 50ul of membrane suspension to the NEN Flash Plate. The resultant assay mixture is incubated for 60 minutes at room temperature followed by addition of 100ul of detection buffer. Plates are then incubated an additional 2-4 hours followed by counting in a Wallac MicroBeta™ scintillation counter. Values of cAMP/well are extrapolated from a standard cAMP curve that is contained within each assay plate.

20 C. Reporter-Based Assays

1. CREB Reporter Assay (Gs-associated receptors)

A method to detect Gs stimulation depends on the known property of the transcription factor CREB, which is activated in a cAMP-dependent manner. A PathDetect™ CREB trans-

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Reporting System (Stratagene, Catalogue # 219010) can utilized to assay for Gs coupled activity in 293 or 293T cells. Cells are transfected with the plasmids components of this above system and the indicated expression plasmid encoding endogenous or mutant receptor using a Mammalian Transfection Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 400 ng pFR-Luc (luciferase reporter plasmid containing Gal4 recognition sequences), 40 ng pFA2-CREB (Gal4-CREB fusion protein containing the Gal4 DNA-binding domain), 80 ng pCMV-receptor expression plasmid (comprising the receptor) and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid; alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the Kit's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells overnight, and replaced with fresh medium the following morning. Forty-eight (48) hr after the start of the transfection, cells are treated and assayed for, *e.g.*, luciferase activity

15 2. AP1 reporter assay (Gq-associated receptors)

A method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing AP1 elements in their promoter. A Pathdetect™ AP-1 cis-Reporting System (Stratagene, Catalogue # 219073) can be utilized following the protocol set forth above with respect to the CREB reporter assay. except that the components of the calcium phosphate precipitate were 410 ng pAP1-Luc. 80 ng pCMV-receptor expression plasmid, and 20 ng CMV-SEAP.

3. CRE-LUC Reporter Assay

293 and 293T cells are plated-out on 96 well plates at a density of 2×10^4 cells per

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well and were transfected using Lipofectamine Reagent (BRL) the following day according to manufacturer instructions. A DNA/lipid mixture is prepared for each 6-well transfection as follows: 260ng of plasmid DNA in 100 μ l of DMEM were gently mixed with 2 μ l of lipid in 100 μ l of DMEM (the 260ng of plasmid DNA consisted of 200ng of a 8xCRE-Luc reporter plasmid (*see* below and Figure 1 for a representation of a portion of the plasmid), 50ng of pCMV comprising endogenous receptor or non-endogenous receptor or pCMV alone, and 10ng of a GPRS expression plasmid (GPRS in pcDNA3 (Invitrogen)). The 8XCRE-Luc reporter plasmid was prepared as follows: vector SRIF- β -gal was obtained by cloning the rat somatostatin promoter (-71/+51) at BglV-HindIII site in the p β gal-Basic Vector (Clontech).

10 Eight (8) copies of cAMP response element were obtained by PCR from an adenovirus template AdpCF126CCRE8 (*see, 7 Human Gene Therapy* 1883 (1996)) and cloned into the SRIF- β -gal vector at the Kpn-BglV site, resulting in the 8xCRE- β -gal reporter vector. The 8xCRE-Luc reporter plasmid was generated by replacing the beta-galactosidase gene in the 8xCRE- β -gal reporter vector with the luciferase gene obtained from the pGL3-basic vector

15 (Promega) at the HindIII-BamHI site. Following 30 min. incubation at room temperature, the DNA/lipid mixture was diluted with 400 μ l of DMEM and 100 μ l of the diluted mixture was added to each well. 100 μ l of DMEM with 10% FCS were added to each well after a 4hr incubation in a cell culture incubator. The following day the transfected cells were changed with 200 μ l/well of DMEM with 10% FCS. Eight (8) hours later, the wells were changed to

20 100 μ l /well of DMEM without phenol red, after one wash with PBS. Luciferase activity were measured the next day using the LucLite™ reporter gene assay kit (Packard) following manufacturer instructions and read on a 1450 MicroBeta™ scintillation and luminescence counter (Wallac).

4. SRF-LUC Reporter Assay

One method to detect Gq stimulation depends on the known property of Gq-dependent phospholipase C to cause the activation of genes containing serum response factors in their promoter. A Pathdetect™ SRF-Luc-Reporting System (Stratagene) can be utilized to assay
5 for Gq coupled activity in, *e.g.*, COS7 cells. Cells are transfected with the plasmid components of the system and the indicated expression plasmid encoding endogenous or non-endogenous GPCR using a Mammalian Transfection™ Kit (Stratagene, Catalogue #200285) according to the manufacturer's instructions. Briefly, 410 ng SRF-Luc, 80 ng pCMV-receptor expression plasmid and 20 ng CMV-SEAP (secreted alkaline phosphatase expression plasmid;
10 alkaline phosphatase activity is measured in the media of transfected cells to control for variations in transfection efficiency between samples) are combined in a calcium phosphate precipitate as per the manufacturer's instructions. Half of the precipitate is equally distributed over 3 wells in a 96-well plate, kept on the cells in a serum free media for 24 hours. The last 5 hours the cells are incubated with 1 μ M Angiotensin, where indicated. Cells are then lysed
15 and assayed for luciferase activity using a Lucite™ Kit (Packard, Cat. # 6016911) and "Trilux 1450 Microbeta" liquid scintillation and luminescence counter (Wallac) as per the manufacturer's instructions. The data can be analyzed using GraphPad Prism™ 2.0a (GraphPad Software Inc.).

5. Intracellular IP₃ Accumulation Assay

20 On day 1, cells comprising the receptors (endogenous and/or non-endogenous) can be plated onto 24 well plates, usually 1×10^5 cells/well (although this number can be optimized. On day 2 cells can be transfected by firstly mixing 0.25 μ g DNA in 50 μ l serum free DMEM/well and 2 μ l lipofectamine in 50 μ l serumfree DMEM/well. The solutions

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are gently mixed and incubated for 15-30 min at room temperature. Cells are washed with 0.5 ml PBS and 400 μ l of serum free media is mixed with the transfection media and added to the cells. The cells are then incubated for 3-4 hrs at 37°C/5%CO₂ and then the transfection media is removed and replaced with 1ml/well of regular growth media. On

5 day 3 the cells are labeled with ³H-myo-inositol. Briefly, the media is removed and the cells are washed with 0.5 ml PBS. Then 0.5 ml inositol-free/serum free media (GIBCO BRL) is added/well with 0.25 μ Ci of ³H-myo-inositol / well and the cells are incubated for 16-18 hrs o/n at 37°C/5%CO₂. On Day 4 the cells are washed with 0.5 ml PBS and 0.45 ml of assay medium is added containing inositol-free/serum free media 10 μ M pargyline

10 10 mM lithium chloride or 0.4 ml of assay medium and 50 μ l of 10x ketanserin (ket) to final concentration of 10 μ M. The cells are then incubated for 30 min at 37°C. The cells are then washed with 0.5 ml PBS and 200 μ l of fresh/icecold stop solution (1M KOH; 18 mM Na-borate; 3.8 mM EDTA) is added/well. The solution is kept on ice for 5-10 min or until cells were lysed and then neutralized by 200 μ l of fresh/ice cold neutralization sol.

15 (7.5 % HCL). The lysate is then transferred into 1.5 ml eppendorf tubes and 1 ml of chloroform/methanol (1:2) is added/tube. The solution is vortexed for 15 sec and the upper phase is applied to a Biorad AG1-X8™ anion exchange resin (100-200 mesh). Firstly, the resin is washed with water at 1:1.25 W/V and 0.9 ml of upper phase is loaded onto the column. The column is washed with 10 mls of 5 mM myo-inositol and 10 ml of 5

20 mM Na-borate/60mM Na-formate. The inositol tris phosphates are eluted into scintillation vials containing 10 ml of scintillation cocktail with 2 ml of 0.1 M formic acid/ 1 M ammonium formate. The columns are regenerated by washing with 10 ml of 0.1 M formic acid/3M ammonium formate and rinsed twice with dd H₂O and stored at 4°C in water.

Exemplary results are presented below in Table I:

TABLE I

| Receptor | Mutation | Assay Utilized | Signal Generated: Endogenous Version (Relative Light Units) | Signal Generated: Non-Endogenous Version (Relative Light Units) | Percent Difference |
|--------------|------------|----------------------|---|---|--------------------|
| hAT1 | F239K | SRF-LUC | 34 | 137 | 75%† |
| | AT2K255IC3 | SRF-LUC | 34 | 127 | 73%† |
| 5 hTDAG8 | I225K | CRE-LUC (293 cells) | 2,715 | 14,440 | 81%† |
| | I225K | CRE-LUC (293T cells) | 65,681 | 185,636 | 65%† |
| hH9 hCCKB | F236K | CRE-LUC | 1,887 | 6,096 | 69%† |
| | V332K | CRE-LUC | 785 | 3,223 | 76%† |

C. CELL-BASED DETECTION ASSAY (EXAMPLE -TDAG8)

10 293 cells were plated-out on 150mm plates at a density of 1.3×10^7 cells per plate, and were transfected using 12ug of the respective DNA and 60ul of Lipofectamine Reagent (BRL) per plate. The transfected cells were grown in media containing serum for an assay performed 24 hours post-transfection. For detection assay performed 48 hours post-transfection (assay comparing serum and serum-free media; see Figure 3), the initial media

15 was changed to either serum or serum-free media. The serum-free media was comprised solely of Dulbecco's Modified Eagle's (DME) High Glucose Medium (Irvine Scientific #9024). In addition to the above DME Medium, the media with serum contained the following: 10% Fetal Bovine Serum (Hyclone #SH30071.03), 1% of 100mM Sodium Pyruvate (Irvine Scientific #9334), 1% of 20mM L-Glutamine (Irvine Scientific #9317), and 1% of Penicillin-

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Streptomycin solution (Irvine Scientific #9366).

A 96-well Adenylyl Cyclase Activation Flashplate™ was used (NEN: #SMP004A). First, 50ul of the standards for the assay were added to the plate, in duplicate, ranging from concentrations of 50pmol to zero pmol cAMP per well. The standard cAMP (NEN: #SMP004A) was reconstituted in water, and serial dilutions were made using 1xPBS (Irvine Scientific: #9240). Next, 50ul of the stimulation buffer (NEN: #SMP004A) was added to all wells. In the case of using compounds to measure activation or inactivation of cAMP, 10ul of each compound, diluted in water, was added to its respective well, in triplicate. Various final concentrations used range from 1uM up to 1mM. Adenosine 5'-triphosphate, ATP, (Research Biochemicals International: #A-141) and Adenosine 5'-diphosphate, ADP, (Sigma: #A2754) were used in the assay. Next, the 293 cells transfected with the respective cDNA (CMV or TDAG8) were harvested 24 (assay detection in serum media) or 48 hours post-transfection (assay detection comparing serum and serum-free media). The media was aspirated and the cells washed once with 1xPBS. Then 5ml of 1xPBS was added to the cells along with 3ml of cell dissociation buffer (Sigma: #C-1544). The detached cells were transferred to a centrifuge tube and centrifuged at room temperature for five minutes. The supernatant was removed and the cell pellet was resuspended in an appropriate amount of 1xPBS to obtain a final concentration of 2×10^6 cells per milliliter. To the wells containing the compound, 50ul of the cells in 1xPBS (1×10^5 cells/well) were added. The plate was incubated on a shaker for 15 minutes at room temperature. The detection buffer containing the tracer cAMP was prepared. In 11ml of detection buffer (NEN: #SMP004A), 50ul (equal to 1uCi) of [125 I]cAMP (NEN: #SMP004A) was added. Following incubation, 50ul of this detection buffer containing tracer cAMP was added to each well. The plate was placed on a shaker and

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incubated at room temperature for two hours. Finally, the solution from the wells of the plate were aspirated and the flashplate was counted using the Wallac MicroBeta™ scintillation counter.

In Figure 2A, ATP and ADP bind to endogenous TDAG8 resulting in an increase of cAMP of about 59% and about 55% respectively. Figure 2B evidences ATP and ADP binding to endogenous TDAG8 where endogenous TDAG8 was transfected and grown in serum and serum-free medium. ATP binding to endogenous TDAG8 grown in serum media evidences an increase in cAMP of about 65%, compared to the endogenous TDAG8 with no compounds; in serum-free media there was an increase of about 68%. ADP binding to endogenous TDAG8 in serum evidences about a 61% increase, while in serum-free ADP binding evidences an increase of about 62% increase. ATP and ADP bind to endogenous TDAG8 with an EC50 value of 139.8uM and 120.5uM, respectively (data not shown).

Although the results presented in Figure 2B indicate substantially the same results when serum and serum-free media were compared, our choice is to use a serum based media, although a serum-free media can also be utilized.

Example 6

GPCR FUSION PROTEIN PREPARATION

The design of the constitutively activated GPCR-G protein fusion construct was accomplished as follows: both the 5' and 3' ends of the rat G protein Gsα (long form; Itoh, H. et al., 83 *PNAS* 3776 (1986)) were engineered to include a HindIII (5'-AAGCTT-3') sequence thereon. Following confirmation of the correct sequence (including the flanking HindIII sequences), the entire sequence was shuttled into pcDNA3.1(-) (Invitrogen, cat. no. V795-20) by subcloning using the HindIII restriction site of that vector. The correct

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orientation for the Gs α sequence was determined after subcloning into pcDNA3.1(-). The modified pcDNA3.1(-) containing the rat Gs α gene at HindIII sequence was then verified; this vector was now available as a "universal" Gs α protein vector. The pcDNA3.1(-) vector contains a variety of well-known restriction sites upstream of the HindIII site, thus
5 beneficially providing the ability to insert, upstream of the Gs protein, the coding sequence of an endogenous, constitutively active GPCR. This same approach can be utilized to create other "universal" G protein vectors, and, of course, other commercially available or proprietary vectors known to the artisan can be utilized – the important criteria is that the sequence for the GPCR be upstream and in-frame with that of the G protein.

10 TDAG8 couples via Gs, while H9 couples via Gz. For the following exemplary GPCR Fusion Proteins, fusion to Gs α was accomplished.

A TDAG8(I225K)-Gs α Fusion Protein construct was made as follows: primers were designed as follows:

5'-gatcTCTAGAATGAACAGCACATGTATTGAAG-3' (SEQ.ID.NO.: 125; sense)

15 5'-ctagGGTACCCGCTCAAGGACCTCTAATTCATAG-3' (SEQ.ID.NO.: 126; antisense).

Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and TDAG8. The sense and anti-sense primers included the restriction sites for XbaI and KpnI, respectively.

PCR was then utilized to secure the respective receptor sequences for fusion within
20 the Gs α universal vector disclosed above, using the following protocol for each: 100ng cDNA for TDAG8 was added to separate tubes containing 2ul of each primer (sense and anti-sense), 3uL of 10mM dNTPs, 10uL of 10XTaqPlus™ Precision buffer, 1uL of TaqPlus™ Precision polymerase (Stratagene: #600211), and 80uL of water. Reaction temperatures and cycle times for TDAG8 were as follows: the initial denaturing step was done at 94°C for five minutes, and

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a cycle of 94°C for 30 seconds; 55°C for 30 seconds; 72°C for two minutes. A final extension time was done at 72°C for ten minutes. PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was digested with XbaI and KpnI (New England Biolabs) and the desired inserts purified and ligated into the Gs universal
5 vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for TDAG8:Gs – Fusion Protein was sequenced to verify correctness.

GPCR Fusion Proteins comprising non-endogenous, constitutively activated
10 TDAG8(I225K) were analyzed as above and verified for constitutive activation.

An H9(F236K)-Gsα Fusion Protein construct was made as follows: primers were designed as follows:

5'-TTAgatattGGGGCCACCCCTAGCGGT-3' (SEQ.ID.NO.: 145; sense)

5'-ggtagcCCCACAGCCATTTCATCAGGATC-3' (SEQ.ID.NO.: 146; antisense).

15 Nucleotides in lower caps are included as spacers in the restriction sites between the G protein and H9. The sense and anti-sense primers included the restriction sites for EcoRV and KpnI, respectively such that spacers (attributed to the restriction sites) exists between the G protein and H9.

PCR was then utilized to secure the respective receptor sequences for fusion within
20 the Gsα universal vector disclosed above, using the following protocol for each: 80ng cDNA for H9 was added to separate tubes containing 100ng of each primer (sense and anti-sense), and 45uL of PCR Supermix™ (Gibco-Brl, LifeTech) (50ul total reaction volume). Reaction temperatures and cycle times for H9 were as follows: the initial denaturing step was done at 94°C for one, and a cycle of 94°C for 30 seconds; 55°C for 30 seconds; 72°C for two

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minutes. A final extension time was done at 72°C for seven minutes. PCR product for was run on a 1% agarose gel and then purified (data not shown). The purified product was cloned into pCRII-TOPO™ System followed by identification of positive clones. Positive clones were isolated, digested with EcoRV and KpnI (New England Biolabs) and the desired inserts were isolated, purified and ligated into the Gs universal vector at the respective restriction site. The positive clones was isolated following transformation and determined by restriction enzyme digest; expression using 293 cells was accomplished following the protocol set forth *infra*. Each positive clone for H9(F236K):Gs – Fusion Protein was sequenced to verify correctness. Membranes were frozen (-80°C) until utilized.

To ascertain the ability of measuring a cAMP response mediated by the Gs protein (even though H9 couples with Gz), the following cAMP membrane assay was utilized, based upon an NEN Adenyl Cyclase Activation Flahplate™ Assay kit (96 well format). "Binding Buffer" consisted of 10mM HEPES, 100mM NaCl and 10mM MgCl (ph 7.4). "Regeneration Buffer" was prepared in Binding Buffer and consisted of 20mM phosphocreatine, 20U creatine phosphokinase, 20uM GTP, 0.2mM ATP, and 0.6mM IBMX. "cAMP Standards" were prepared in Binding Buffer as follows:

| | | cAMP Stock (5,000 pmol/ml in 2ml H ₂ O) in ul | Added to indicted amount of Binding Buffer | Final Assay Concentration (50ul into 100ul) to achieve indicated pmol/well |
|----|---|--|--|--|
| 20 | A | 250 | 1ml | 50 |
| | B | 500 of A | 500ul | 25 |
| | C | 500 of B | 500ul | 12.5 |
| | D | 500 of C | 750ul | 5.0 |
| | E | 500 of D | 500ul | 2.5 |
| 25 | F | 500 of E | 500ul | 1.25 |
| | G | 500 of F | 750ul | 0.5 |

Frozen membranes (both pCMV as control and the non-endogenous H(-Gs Fusion Protein) were thawed (on ice at room temperature until in solution). Membranes were

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homogenized with a polytron until in suspension (2 x 15 seconds). Membrane protein concentration was determined using the Bradford Assay Protocol (*see infra*). Membrane concentration was diluted to 0.5mg/ml in Regeneration Buffer (final assay concentration – 25ug/well). Thereafter, 50ul of Binding Buffer was added to each well. For control, 50ul/well of cAMP standard was added to wells 11 and 12 A-G, with Binding Buffer alone to 12H (on the 96-well format). Thereafter, 50ul/well of protein was added to the wells and incubated at room temperature (on shaker) for 60min. 100ul [¹²⁵I]cAMP in Detection Buffer (*see infra*) was added to each well (final – 50ul [¹²⁵I]cAMP into 11ml Detection Buffer). These were incubated for 2hrs at room temperature. Plates were aspirated with an 8 channel manifold and sealed with plate covers. Results (pmoles cAMP bound) were read in a Wallac™ 1450 on "prot #15). Results are presented in Figure 3.

The results presented in Figure 3 indicate that the Gs coupled fusion was able to "drive" the cyclase reaction such that measurement of the constitutive activation of H9(F236K) was viable. Based upon these results, the direct identification of candidate compounds that are inverse agonists, agonists and partial agonists is possible using a cyclase-based assay.

Example 6

Protocol: Direct Identification of Inverse Agonists and Agonists Using [³⁵S]GTPγS

Although we have utilized endogenous, constitutively active GPCRs for the direct identification of candidate compounds as, *e.g.*, inverse agonists, for reasons that are not altogether understood, intra-assay variation can become exacerbated. Preferably, then, a GPCR Fusion Protein, as disclosed above, is also utilized with a non-endogenous, constitutively activated GPCR. We have determined that when such a protein is used, intra-assay variation appears to be substantially stabilized, whereby an effective signal-to-noise ratio is obtained. This has the beneficial result of allowing for a more robust identification

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of candidate compounds. Thus, it is preferred that for direct identification, a GPCR Fusion Protein be used and that when utilized, the following assay protocols be utilized.

Membrane Preparation

Membranes comprising the non-endogenous, constitutively active orphan GPCR Fusion Protein of interest and for use in the direct identification of candidate compounds as inverse agonists, agonists or partial agonists are preferably prepared as follows:

a. Materials

"Membrane Scrape Buffer" is comprised of 20mM HEPES and 10mM EDTA, pH 7.4;

"Membrane Wash Buffer" is comprised of 20 mM HEPES and 0.1 mM EDTA, pH 7.4;

10 "Binding Buffer" is comprised of 20mM HEPES, 100 mM NaCl, and 10 mM MgCl₂, pH 7.4

b. Procedure

All materials are kept on ice throughout the procedure. Firstly, the media is aspirated from a confluent monolayer of cells, followed by rinse with 10ml cold PBS, followed by aspiration. Thereafter, 5ml of Membrane Scrape Buffer is added to scrape cells; this is followed by transfer of cellular extract into 50ml centrifuge tubes (centrifuged at 20,000 rpm for 17 minutes at 4°C). Thereafter, the supernatant is aspirated and the pellet is resuspended in 30ml Membrane Wash Buffer followed by centrifuge at 20,000 rpm for 17 minutes at 4°C. The supernatant is then aspirated and the pellet resuspended in Binding Buffer. This is then homogenized using a Brinkman polytron™ homogenizer (15-20 second bursts until the all material is in suspension). This is referred to herein as "Membrane Protein".

Bradford Protein Assay

Following the homogenization, protein concentration of the membranes is determined using the Bradford Protein Assay (protein can be diluted to about 1.5mg/ml, aliquoted and

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frozen (-80°C) for later use; when frozen, protocol for use is as follows: on the day of the assay, frozen Membrane Protein is thawed at room temperature, followed by vortex and then homogenized with a polytron at about 12 x 1,000 rpm for about 5-10 seconds; it is noted that for multiple preparations, the homogenizer should be thoroughly cleaned between
5 homogenization of different preparations).

a. Materials

Binding Buffer (as per above); Bradford Dye Reagent; Bradford Protein Standard are utilized, following manufacturer instructions (Biorad, cat. no. 500-0006).

b. Procedure

10 Duplicate tubes are prepared, one including the membrane, and one as a control "blank". Each contained 800ul Binding Buffer. Thereafter, 10ul of Bradford Protein Standard (1mg/ml) is added to each tube, and 10ul of membrane Protein is then added to just one tube (not the blank). Thereafter, 200ul of Bradford Dye Reagent is added to each tube, followed by vortex of each. After five (5) minutes, the tubes were re-vortexed and the material therein
15 is transferred to cuvettes. The cuvettes are then read using a CECIL 3041 spectrophotometer, at wavelength 595.

Direct Identification Assay

a. Materials

GDP Buffer consists of 37.5 ml Binding Buffer and 2mg GDP (Sigma, cat. no. G-
20 7127), followed by a series of dilutions in Binding Buffer to obtain 0.2 uM GDP (final concentration of GDP in each well was 0.1 uM GDP); each well comprising a candidate compound, has a final volume of 200ul consisting of 100ul GDP Buffer (final concentration, 0.1uM GDP), 50ul Membrane Protein in Binding Buffer, and 50ul [³⁵S]GTPγS (0.6 nM) in

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Binding Buffer (2.5 ul [³⁵S]GTPγS per 10ml Binding Buffer).

b. Procedure

Candidate compounds are preferably screened using a 96-well plate format (these can be frozen at -80°C). Membrane Protein (or membranes with expression vector excluding the GPCR Fusion Protein, as control), are homogenized briefly until in suspension. Protein concentration is then determined using the Bradford Protein Assay set forth above. Membrane Protein (and control) is then diluted to 0.25mg/ml in Binding Buffer (final assay concentration, 12.5ug/well). Thereafter, 100 ul GDP Buffer is added to each well of a Wallac Scintistrip™ (Wallac). A 5ul pin-tool is then used to transfer 5 ul of a candidate compound into such well (*i.e.*, 5ul in total assay volume of 200 ul is a 1:40 ratio such that the final screening concentration of the candidate compound is 10uM). Again, to avoid contamination, after each transfer step the pin tool should be rinsed in three reservoirs comprising water (1X), ethanol (1X) and water (2X) – excess liquid should be shaken from the tool after each rinse and dried with paper and kimwipes. Thereafter, 50 ul of Membrane Protein is added to each well (a control well comprising membranes without the GPCR Fusion Protein is also utilized), and pre-incubated for 5-10 minutes at room temperature. Thereafter, 50 ul of [³⁵S]GTPγS (0.6 nM) in Binding Buffer is added to each well, followed by incubation on a shaker for 60 minutes at room temperature (again, in this example, plates were covered with foil). The assay is then stopped by spinning of the plates at 4000 RPM for 15 minutes at 22°C. The plates are then aspirated with an 8 channel manifold and sealed with plate covers. The plates are then read on a Wallacc 1450 using setting "Prot. #37" (as per manufacturer instructions).

Example 7

Protocol: Confirmation Assay

Using an independent assay approach to provide confirmation of a directly identified

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candidate compound as set forth above, it is preferred that a confirmation assay then be utilized. In this case, the preferred confirmation assay is a cyclase-based assay.

A modified Flash Plate™ Adenylyl Cyclase kit (New England Nuclear; Cat. No. SMP004A) is preferably utilized for confirmation of candidate compounds directly identified
5 as inverse agonists and agonists to non-endogenous, constitutively activated orphan GPCRs in accordance with the following protocol.

Transfected cells are harvested approximately three days after transfection. Membranes are prepared by homogenization of suspended cells in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCl₂. Homogenization is performed on ice using a Brinkman
10 Polytron™ for approximately 10 seconds. The resulting homogenate is centrifuged at 49,000 X g for 15 minutes at 4°C. The resulting pellet is then resuspended in buffer containing 20mM HEPES, pH 7.4 and 0.1 mM EDTA, homogenized for 10 seconds, followed by centrifugation at 49,000 X g for 15 minutes at 4°C. The resulting pellet can be stored at -80°C until utilized. On the day of direct identification screening, the membrane pellet is
15 slowly thawed at room temperature, resuspended in buffer containing 20mM HEPES, pH 7.4 and 10mM MgCL₂, to yield a final protein concentration of 0.60mg/ml (the resuspended membranes are placed on ice until use).

cAMP standards and Detection Buffer (comprising 2 μCi of tracer [¹²⁵I cAMP (100 μl] to 11 ml Detection Buffer) are prepared and maintained in accordance with the
20 manufacturer's instructions. Assay Buffer is prepared fresh for screening and contained 20mM HEPES, pH 7.4, 10mM MgCl₂, 20mM phosphocreatine (Sigma), 0.1 units/ml creatine phosphokinase (Sigma), 50 μM GTP (Sigma), and 0.2 mM ATP (Sigma); Assay Buffer can be stored on ice until utilized.

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Candidate compounds identified as per above (if frozen, thawed at room temperature) are added, preferably, to 96-well plate wells ($3\mu\text{l}$ /well; $12\mu\text{M}$ final assay concentration), together with $40\mu\text{l}$ Membrane Protein ($30\mu\text{g}$ /well) and $50\mu\text{l}$ of Assay Buffer. This admixture is then incubated for 30 minutes at room temperature, with gentle shaking.

5 Following the incubation, $100\mu\text{l}$ of Detection Buffer is added to each well, followed by incubation for 2-24 hours. Plates are then counted in a Wallac MicroBeta™ plate reader using "Prot. #31" (as per manufacturer instructions).

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

10 As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

Although a variety of expression vectors are available to those in the art, for purposes of utilization for both the endogenous and non-endogenous human GPCRs, it is most preferred that the vector utilized be pCMV. This vector was deposited with the American Type Culture Collection (ATCC) on October 13, 1998 (10801 University Blvd., Manassas, VA 20110-2209 USA) under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The DNA was tested by the ATCC and determined to be. The ATCC has
15
20 assigned the following deposit number to pCMV: ATCC #203351.

CLAIMS

What is claimed is:

1. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-3(F313K).
- 5 2. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 1.
3. A Plasmid comprising a Vector and the cDNA of claim 1.
4. A Host Cell comprising the Plasmid of claim 3.
5. A cDNA encoding a non-endogenous, constitutively activated version of a human
- 10 G protein-coupled receptor comprising hARE-4(V233K)
6. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 5.
7. A Plasmid comprising a Vector and the cDNA of claim 5.
8. A Host Cell comprising the Plasmid of claim 7.
- 15 9. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-5(A240K).
10. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 9.
11. A Plasmid comprising a Vector and the cDNA of claim 5.
- 20 12. A Host Cell comprising the Plasmid of claim 11.
13. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR14(L257K).

14. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 13.
15. A Plasmid comprising a Vector and the cDNA of claim 13.
- 5 16. A Host Cell comprising the Plasmid of claim 15.
17. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hGPCR27(C283K).
18. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 17.
- 10 19. A Plasmid comprising a Vector and the cDNA of claim 17.
20. A Host Cell comprising the Plasmid of claim 19.
21. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-1(E232K).
22. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 21.
- 15 23. A Plasmid comprising a Vector and the cDNA of claim 21.
24. A Host Cell comprising the Plasmid of claim 23.
25. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hARE-2(G285K).
- 20 26. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 25.
27. A Plasmid comprising a Vector and the cDNA of claim 25.
28. A Host Cell comprising the Plasmid of claim 27.

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29. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hPPR1(L239K).
30. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 29.
- 5 31. A Plasmid comprising a Vector and the cDNA of claim 29.
32. A Host Cell comprising the Plasmid of claim 31.
33. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hG2A(K232A).
34. A non-endogenous version of a human G protein-coupled receptor encoded by the
10 cDNA of claim 33.
35. A Plasmid comprising a Vector and the cDNA of claim 33.
36. A Host Cell comprising the Plasmid of claim 35.
37. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hRUP3(L224K).
- 15 38. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 37.
39. A Plasmid comprising a Vector and the cDNA of claim 37.
40. A Host Cell comprising the Plasmid of claim 39.
41. A cDNA encoding a non-endogenous, constitutively activated version of a human
20 G protein-coupled receptor comprising hRUP5(A236K).
42. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 41.
43. A Plasmid comprising a Vector and the cDNA of claim 41.

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44. A Host Cell comprising the Plasmid of claim 42.
45. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hRUP6(N267K)
46. A non-endogenous version of a human G protein-coupled receptor encoded by the
5 cDNA of claim 45.
47. A Plasmid comprising a Vector and the cDNA of claim 45.
48. A Host Cell comprising the Plasmid of claim 47.
49. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hRUP7(A302K).
- 10 50. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 49.
51. A Plasmid comprising a Vector and the cDNA of claim 49.
52. A Host Cell comprising the Plasmid of claim 51.
53. A cDNA encoding a non-endogenous, constitutively activated version of a human
15 G protein-coupled receptor comprising hCHN4(V236K).
54. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 53.
55. A Plasmid comprising a Vector and the cDNA of claim 53.
56. A Host Cell comprising the Plasmid of claim 55.
- 20 57. A cDNA encoding a non-endogenous, constitutively activated version of a human
G protein-coupled receptor comprising hMC4(A244K).
58. A non-endogenous version of a human G protein-coupled receptor encoded by the
cDNA of claim 57.

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59. A Plasmid comprising a Vector and the cDNA of claim 57.
60. A Host Cell comprising the Plasmid of claim 60.
61. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN3(S284K).
- 5 62. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 61.
63. A Plasmid comprising a Vector and the cDNA of claim 61.
64. A Host Cell comprising the Plasmid of claim 63.
65. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN6(L352K).
- 10 66. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 65.
67. A Plasmid comprising a Vector and the cDNA of claim 65.
68. A Host Cell comprising the Plasmid of claim 67.
- 15 69. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hCHN8(N235K).
70. A non-endogenous version of a human G protein-coupled receptor encoded by the cDNA of claim 69.
71. A Plasmid comprising a Vector and the cDNA of claim 69.
- 20 72. A Host Cell comprising the Plasmid of claim 71.
73. A cDNA encoding a non-endogenous, constitutively activated version of a human G protein-coupled receptor comprising hH9(F236K).
74. A non-endogenous version of a human G protein-coupled receptor encoded by the

- 67 -

cDNA of claim 73.

75. A Plasmid comprising a Vector and the cDNA of claim 73.

76. A Host Cell comprising the Plasmid of claim 74.

77. A cDNA encoding a non-endogenous, constitutively activated version of a human

5 G protein-coupled AT1 receptor selected from the group consisting of:

hAT1(F239K); hAT1(N111A); hAT1(AT2K255IC3); and hAT1(A243+).

78. A non-endogenous version of a human G protein-coupled receptor encoded by a
cDNA of claim 77.

79. A Plasmid comprising a Vector and the cDNA of claim 77.

10 80. A Host Cell comprising the Plasmid of claim 79.

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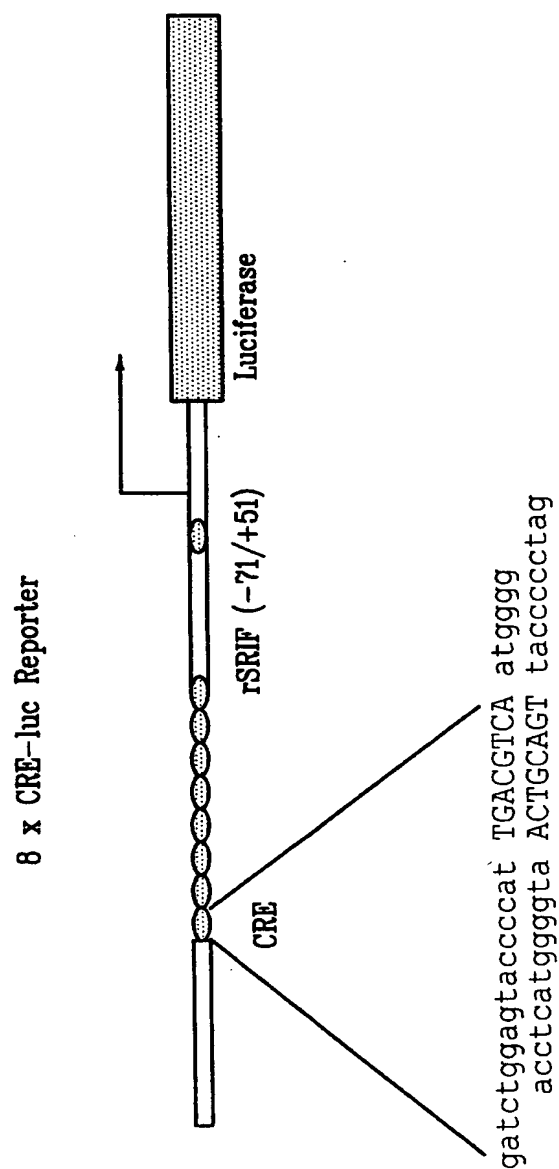


FIG. 1

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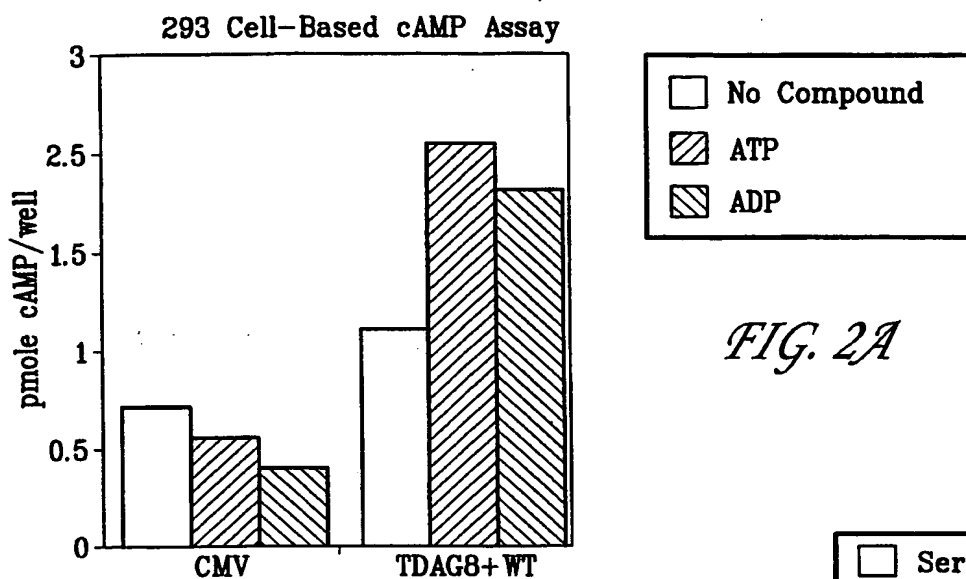


FIG. 2A

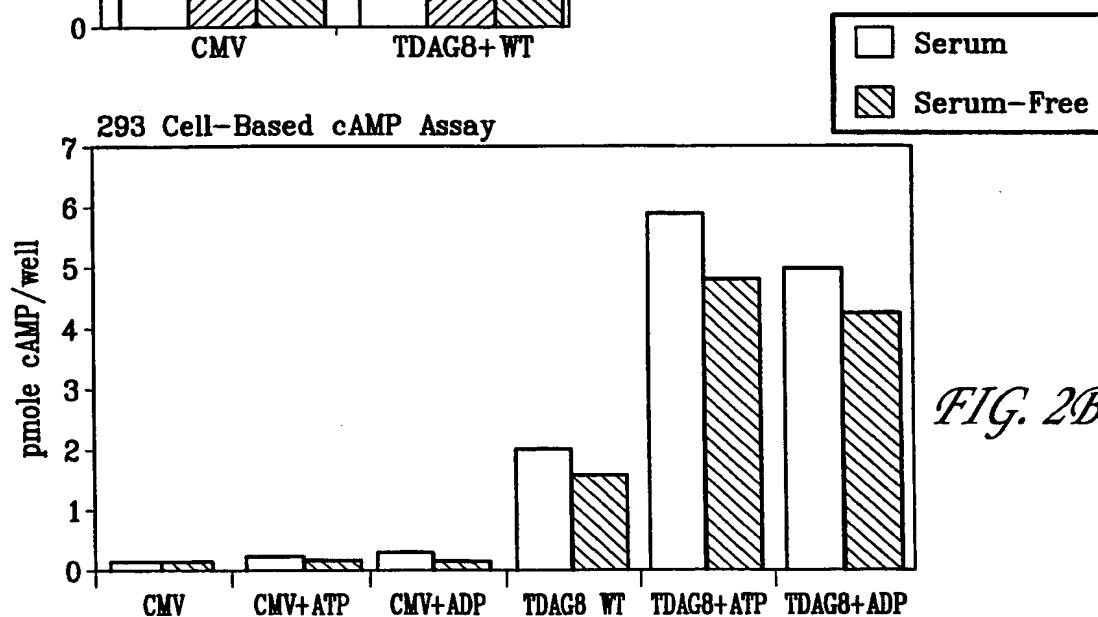


FIG. 2B

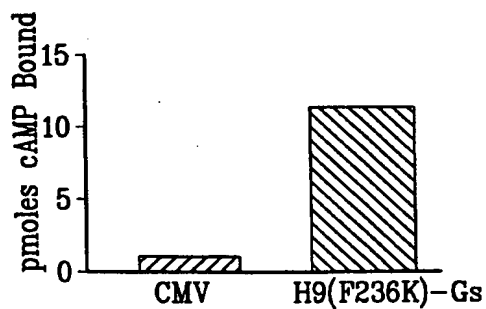


FIG. 3

- 1 -

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Behan, Dominic P.
Lehmann-Bruinsma, Karin
Chalmers, Derek T.
Lowitz, Kevin P.
Lin, I-Lin
Dang, Huong T.
10 Chen, Ruoping
Liaw, Chen W.
Gore, Martin J.
White, Carol
- 15 (ii) TITLE OF INVENTION: Non-Endogenous, Constitutively Activated Human G
Protein-Coupled Receptors
- (iii) NUMBER OF SEQUENCES: 146
- 20 (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Arena Pharmaceuticals, Inc.
(B) STREET: 6166 Nancy Ridge Drive
(C) CITY: San Diego
(D) STATE: CA
(E) COUNTRY: USA
(F) ZIP: 92121
- 25 (v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- 30 (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US
(B) FILING DATE:
(C) CLASSIFICATION:
- 35 (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Burgoon, Richard P.
(B) REGISTRATION NUMBER: 34,787
- (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (858)453-7200
(B) TELEFAX: (858)453-7210
- 40 (2) INFORMATION FOR SEQ ID NO:1:
- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1260 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

| | | | | | | | |
|----|------------|-------------|------------|------------|------------|------------|------|
| | ATGGTCTTCT | CGGCAGTGTT | GACTGCGTTC | CATACCGGGA | CATCCAACAC | AACATTTGTC | 60 |
| 5 | GTGTATGAAA | ACACCTACAT | GAATATTACA | CTCCCTCCAC | CATTCCAGCA | TCCTGACCTC | 120 |
| | AGTCCATTGC | TTAGATATAG | TTTGAAACC | ATGGCTCCCA | CTGGTTTGAG | TTCCTTGACC | 180 |
| | GTGAATAGTA | CAGCTGTGCC | CACAACACCA | GCAGCATTTA | AGAGCCTAAA | CTTGCTCTT | 240 |
| | CAGATCACCC | TTTCTGCTAT | AATGATATTC | ATTCTGTTTG | TGTCTTTTCT | TGGGAACCTG | 300 |
| | GTTGTTTGCC | TCATGGTTTA | CCAAAAGCT | GCCATGAGGT | CTGCAATTAA | CATCCTCCTT | 360 |
| 10 | GCCAGCCTAG | CTTTTGACAGA | CATGTTGCTT | GCAGTGCTGA | ACATGCCCTT | TGCCCTGGTA | 420 |
| | ACTATTCTTA | CTACCCGATG | GATTTTGGG | AAATTCTTCT | GTAGGGTATC | TGCTATGTTT | 480 |
| | TTCTGGTTAT | TTGTGATAGA | AGGAGTAGCC | ATCCTGCTCA | TCATTAGCAT | AGATAGGTTC | 540 |
| | CTTATTATAG | TCCAGAGGCA | GGATAAGCTA | AACCCATATA | GAGCTAAGGT | TCTGATTGCA | 600 |
| | GTTTCTTGGG | CAACTTCCTT | TTGTGTAGCT | TTTCCTTTAG | CCGTAGGAAA | CCCCGACCTG | 660 |
| 15 | CAGATACCTT | CCCGAGCTCC | CCAGTGTGTG | TTTGGGTACA | CAACCAATCC | AGGCTACCAG | 720 |
| | GCTTATGTGA | TTTTGATTTC | TCTCATTTCT | TTCTTCATAC | CCTTCCTGGT | AATACTGTAC | 780 |
| | TCATTTATGG | GCATACTCAA | CACCCTTCGG | CACAATGCCT | TGAGGATCCA | TAGCTACCCT | 840 |
| | GAAGGTATAT | GCCTCAGCCA | GGCCAGCAAA | CTGGGTCTCA | TGAGTCTGCA | GAGACCTTTC | 900 |
| | CAGATGAGCA | TTGACATGGG | CTTTAAAACA | CGTGCCCTCA | CCACTATTTT | GATTCTCTTT | 960 |
| 20 | GCTGTCTTCA | TTGTCTGCTG | GGCCCCATTC | ACCACTTACA | GCCTTGTGGC | AACATTCAGT | 1020 |
| | AAGCACTTTT | ACTATCAGCA | CAACTTTTTT | GAGATTAGCA | CCTGGCTACT | GTGGCTCTGC | 1080 |
| | TACCTCAAGT | CTGCATTGAA | TCCGCTGATC | TACTACTGGA | GGATTAAGAA | ATTCCATGAT | 1140 |
| | GCTTGCCTGG | ACATGATGCC | TAAGTCCTTC | AAGTTTTTGC | CGCAGCTCCC | TGGTCACACA | 1200 |
| | AAGCGACGGA | TACGTCCTAG | TGCTGTCTAT | GTGTGTGGGG | AACATCGGAC | GGTGGTGTGA | 1260 |

25 (3) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 419 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

30 (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Met | Val | Phe | Ser | Ala | Val | Leu | Thr | Ala | Phe | His | Thr | Gly | Thr | Ser | Asn | |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| 5 | Thr | Thr | Phe | Val | Val | Tyr | Glu | Asn | Thr | Tyr | Met | Asn | Ile | Thr | Leu | Pro | |
| | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | Pro | Pro | Phe | Gln | His | Pro | Asp | Leu | Ser | Pro | Leu | Leu | Arg | Tyr | Ser | Phe | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| 10 | Glu | Thr | Met | Ala | Pro | Thr | Gly | Leu | Ser | Ser | Leu | Thr | Val | Asn | Ser | Thr | |
| | | 50 | | | | | 55 | | | | | 60 | | | | | |
| | Ala | Val | Pro | Thr | Thr | Pro | Ala | Ala | Phe | Lys | Ser | Leu | Asn | Leu | Pro | Leu | |
| | 65 | | | | | 70 | | | | 75 | | | | | | 80 | |
| | Gln | Ile | Thr | Leu | Ser | Ala | Ile | Met | Ile | Phe | Ile | Leu | Phe | Val | Ser | Phe | |
| | | | | 85 | | | | | | 90 | | | | | 95 | | |
| 15 | Leu | Gly | Asn | Leu | Val | Val | Cys | Leu | Met | Val | Tyr | Gln | Lys | Ala | Ala | Met | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| | Arg | Ser | Ala | Ile | Asn | Ile | Leu | Leu | Ala | Ser | Leu | Ala | Phe | Ala | Asp | Met | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| 20 | Leu | Leu | Ala | Val | Leu | Asn | Met | Pro | Phe | Ala | Leu | Val | Thr | Ile | Leu | Thr | |
| | | 130 | | | | | 135 | | | | | 140 | | | | | |
| | Thr | Arg | Trp | Ile | Phe | Gly | Lys | Phe | Phe | Cys | Arg | Val | Ser | Ala | Met | Phe | |
| | 145 | | | | | 150 | | | | 155 | | | | | 160 | | |
| | Phe | Trp | Leu | Phe | Val | Ile | Glu | Gly | Val | Ala | Ile | Leu | Leu | Ile | Ile | Ser | |
| | | | | 165 | | | | | 170 | | | | | | 175 | | |
| 25 | Ile | Asp | Arg | Phe | Leu | Ile | Ile | Val | Gln | Arg | Gln | Asp | Lys | Leu | Asn | Pro | |
| | | | 180 | | | | | | 185 | | | | | 190 | | | |
| | Tyr | Arg | Ala | Lys | Val | Leu | Ile | Ala | Val | Ser | Trp | Ala | Thr | Ser | Phe | Cys | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| 30 | Val | Ala | Phe | Pro | Leu | Ala | Val | Gly | Asn | Pro | Asp | Leu | Gln | Ile | Pro | Ser | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | Arg | Ala | Pro | Gln | Cys | Val | Phe | Gly | Tyr | Thr | Thr | Asn | Pro | Gly | Tyr | Gln | |
| | 225 | | | | 230 | | | | | | 235 | | | | | 240 | |
| | Ala | Tyr | Val | Ile | Leu | Ile | Ser | Leu | Ile | Ser | Phe | Phe | Ile | Pro | Phe | Leu | |
| | | | | 245 | | | | | 250 | | | | | 255 | | | |
| 35 | Val | Ile | Leu | Tyr | Ser | Phe | Met | Gly | Ile | Leu | Asn | Thr | Leu | Arg | His | Asn | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |

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Ala Leu Arg Ile His Ser Tyr Pro Glu Gly Ile Cys Leu Ser Gln Ala
275 280 285

Ser Lys Leu Gly Leu Met Ser Leu Gln Arg Pro Phe Gln Met Ser Ile
290 295 300

5 Asp Met Gly Phe Lys Thr Arg Ala Phe Thr Thr Ile Leu Ile Leu Phe
305 310 315 320

Ala Val Phe Ile Val Cys Trp Ala Pro Phe Thr Thr Tyr Ser Leu Val
325 330 335

10 Ala Thr Phe Ser Lys His Phe Tyr Tyr Gln His Asn Phe Phe Glu Ile
340 345 350

Ser Thr Trp Leu Leu Trp Leu Cys Tyr Leu Lys Ser Ala Leu Asn Pro
355 360 365

Leu Ile Tyr Tyr Trp Arg Ile Lys Lys Phe His Asp Ala Cys Leu Asp
370 375 380

15 Met Met Pro Lys Ser Phe Lys Phe Leu Pro Gln Leu Pro Gly His Thr
385 390 395 400

Lys Arg Arg Ile Arg Pro Ser Ala Val Tyr Val Cys Gly Glu His Arg
405 410 415

Thr Val Val

20

(4) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1119 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 25

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATGTTAGCCA ACAGTCCTC AACCAACAGT TCTGTTCTCC CGTGTCTCTGA CTACCGACCT 60

30 ACCCACC GCC TGA CTTGGT GGTCTACAGC TTGGTGCTGG CTGCCGGGCT CCCCTCAAC 120

GCGCTAGCCC TCTGGGTCTT CCTGCGCGCG CTGCGCGTGC ACTCGGTGGT GAGCGTGTAC 180

ATGTGTAACC TGGCGGCCAG CGACCTGCTC TTCACCCTCT CGCTGCCCCT TCGTCTCTCC 240

TACTACGCAC TGCACCACTG GCCCTTCCCC GACCTCCTGT GCCAGACGAC GGGCGCCATC 300

TTCCAGATGA ACATGTACGG CAGCTGCATC TTCCTGATGC TCATCAACGT GGACCGCTAC 360

- 5 -

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GCCGCCATCG TGCACCCGCT GCGACTGCGC CACCTGCGGC GGCCCCGCGT GGCGCGGCTG      420
CTCTGCCTGG GCGTGTGGGC GCTCATCCTG GTGTTTGCCG TGCCCGCCGC CCGCGTGAC      480
AGGCCCTCGC GTTGCCGCTA CCGGGACCTC GAGGTGCGCC TATGCTTCGA GAGCTTCAGC      540
GACGAGCTGT GGAAAGGCAG GCTGCTGCCC CTCGTGCTGC TGGCCGAGGC GCTGGGCTTC      600
5 CTGCTGCCCC TGGCGGCGGT GGTCTACTCG TCGGGCCGAG TCTTCTGGAC GCTGGCGCGC      660
CCCGACGCCA CGCAGAGCCA GCGGCGGCGG AAGACCGTGC GCCTCCTGCT GGCTAACCTC      720
GTCATCTTCC TGCTGTGCTT CGTGCCCTAC AACAGCACGC TGGCGGTCTA CGGGCTGCTG      780
CGGAGCAAGC TGGTGGCGGC CAGCGTGCCT GCCCGCGATC GCGTGCGCGG GGTGCTGATG      840
GTGATGGTGC TGCTGGCCGG CGCCAACTGC GTGCTGGACC CGCTGGTGTA CTACTTTAGC      900
10 GCCGAGGGCT TCCGCAACAC CCTGCGCGGC CTGGGCACTC CGCACCAGGC CAGGACCTCG      960
GCCACCAACG GGACGCGGGC GCGGCTCGCG CAATCCGAAA GGTCCGCCGT CACCACCGAC      1020
GCCACCAGGC CGGATGCCGC CAGTCAGGGG CTGCTCCGAC CCTCCGACTC CCACTCTCTG      1080
TCTTCCTTCA CACAGTGTCC CCAGGATTCC GCCCTCTGA      1119

```

(5) INFORMATION FOR SEQ ID NO:4:

- 15 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 372 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant

- 20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Met Leu Ala Asn Ser Ser Ser Thr Asn Ser Ser Val Leu Pro Cys Pro
1           5           10           15

Asp Tyr Arg Pro Thr His Arg Leu His Leu Val Val Tyr Ser Leu Val
25          20          25          30

Leu Ala Ala Gly Leu Pro Leu Asn Ala Leu Ala Leu Trp Val Phe Leu
35          40          45

Arg Ala Leu Arg Val His Ser Val Val Ser Val Tyr Met Cys Asn Leu
50          55          60

30 Ala Ala Ser Asp Leu Leu Phe Thr Leu Ser Leu Pro Val Arg Leu Ser
65          70          75          80

Tyr Tyr Ala Leu His His Trp Pro Phe Pro Asp Leu Leu Cys Gln Thr

```

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| | 85 | 90 | 95 |
|----|---|-----|-----|
| | Thr Gly Ala Ile Phe Gln Met Asn Met Tyr Gly Ser Cys Ile Phe Leu | | |
| | 100 | 105 | 110 |
| 5 | Met Leu Ile Asn Val Asp Arg Tyr Ala Ala Ile Val His Pro Leu Arg | | |
| | 115 | 120 | 125 |
| | Leu Arg His Leu Arg Arg Pro Arg Val Ala Arg Leu Leu Cys Leu Gly | | |
| | 130 | 135 | 140 |
| | Val Trp Ala Leu Ile Leu Val Phe Ala Val Pro Ala Ala Arg Val His | | |
| | 145 | 150 | 155 |
| 10 | Arg Pro Ser Arg Cys Arg Tyr Arg Asp Leu Glu Val Arg Leu Cys Phe | | |
| | 165 | 170 | 175 |
| | Glu Ser Phe Ser Asp Glu Leu Trp Lys Gly Arg Leu Leu Pro Leu Val | | |
| | 180 | 185 | 190 |
| 15 | Leu Leu Ala Glu Ala Leu Gly Phe Leu Leu Pro Leu Ala Ala Val Val | | |
| | 195 | 200 | 205 |
| | Tyr Ser Ser Gly Arg Val Phe Trp Thr Leu Ala Arg Pro Asp Ala Thr | | |
| | 210 | 215 | 220 |
| | Gln Ser Gln Arg Arg Arg Lys Thr Val Arg Leu Leu Leu Ala Asn Leu | | |
| | 225 | 230 | 235 |
| 20 | Val Ile Phe Leu Leu Cys Phe Val Pro Tyr Asn Ser Thr Leu Ala Val | | |
| | 245 | 250 | 255 |
| | Tyr Gly Leu Leu Arg Ser Lys Leu Val Ala Ala Ser Val Pro Ala Arg | | |
| | 260 | 265 | 270 |
| 25 | Asp Arg Val Arg Gly Val Leu Met Val Met Val Leu Leu Ala Gly Ala | | |
| | 275 | 280 | 285 |
| | Asn Cys Val Leu Asp Pro Leu Val Tyr Tyr Phe Ser Ala Glu Gly Phe | | |
| | 290 | 295 | 300 |
| | Arg Asn Thr Leu Arg Gly Leu Gly Thr Pro His Arg Ala Arg Thr Ser | | |
| | 305 | 310 | 315 |
| 30 | Ala Thr Asn Gly Thr Arg Ala Ala Leu Ala Gln Ser Glu Arg Ser Ala | | |
| | 325 | 330 | 335 |
| | Val Thr Thr Asp Ala Thr Arg Pro Asp Ala Ala Ser Gln Gly Leu Leu | | |
| | 340 | 345 | 350 |
| 35 | Arg Pro Ser Asp Ser His Ser Leu Ser Ser Phe Thr Gln Cys Pro Gln | | |
| | 355 | 360 | 365 |
| | Asp Ser Ala Leu | | |
| | 370 | | |

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(6) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1107 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```

ATGGCCAACT CCACAGGGCT GAACGCCTCA GAAGTCGCAG GCTCGTTGGG GTTGATCCTG      60
10 GCAGCTGTCG TGGAGGTGGG GGCAGTCTG GGCACCGGCG CGCTGCTGGT CGTGGTGCTG      120
   CGCACGCCGG GACTGCGCGA CGCGCTCTAC CTGGCGCACC TGTGCGTCGT GGACCTGCTG      180
   GCGGCCCGCT CCATCATGCC GCTGGGCCCTG CTGGCCGCAC CGCCGCCCGG GCTGGGCCGC      240
   GTGCGCCTGG GCCCCGCGCC ATGCCGCGCC GCTCGCTTCC TCTCCGCCGC TCTGCTGCCG      300
   GCCTGCACGC TCGGGGTGGC CGCACTTGGC CTGGCACGCT ACCGCCTCAT CGTGCACCCG      360
15 CTGCGGCCAG GCTCGCGGCC GCCGCCTGTG CTCGTGCTCA CCGCCGTGTG GGCCGCGGCG      420
   GGACTGCTGG GCGCGCTCTC CCTGCTCGGC CCGCCGCCCG CACCGCCCCC TGCTCCTGCT      480
   CGCTGCTCGG TCCTGGCTGG GGGCCTCGGG CCCTTCCGGC CGCTCTGGGC CCTGCTGGCC      540
   TTCGCGCTGC CCGCCCTCCT GCTGCTCGGC GCCTACGGCG GCATCTTCGT GGTGGCGCGT      600
   CGCGCTGCCC TGAGGCCCCC ACGGCCGGCG CGCGGGTCCC GACTCCGCTC GGACTCTCTG      660
20 GATAGCCGCC TTTCCATCTT GCCGCCGCTC CGGCCTCGCC TGCCCGGGGG CAAGGCGGCC      720
   CTGGCCCCAG CGCTGGCCGT GGGCCAATTT GCAGCCTGCT GGCTGCCTTA TGGCTGCGCG      780
   TGCCTGGCGC CCGCAGCGCG GGCCGCGGAA GCCGAAGCGG CTGTCACCTG GGTCGCCTAC      840
   TCGGCCTTCG CGGCTCACCC CTTCCTGTAC GGGCTGCTGC AGCGCCCCGT GCGCTTGGCA      900
   CTGGGCCGCC TCTCTCGCCG TGCACTGCCT GGACCTGTGC GGGCCTGCAC TCCGCAAGCC      960
25 TGGCACCCGC GGGCACTCTT GCAATGCCTC CAGAGACCCC CAGAGGGCCC TGCCGTAGGC      1020
   CCTTCTGAGG CTCCAGAACA GACCCCGAG TTGGCAGGAG GGCGGAGCCC CGCATACCAG      1080
   GGGCCACCTG AGAGTTCTCT CTCCTGA                                     1107

```

(7) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 368 amino acids

- 8 -

(B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ala | Asn | Ser | Thr | Gly | Leu | Asn | Ala | Ser | Glu | Val | Ala | Gly | Ser | Leu | 1 | 5 | 10 | 15 |
| Gly | Leu | Ile | Leu | Ala | Ala | Val | Val | Glu | Val | Gly | Ala | Leu | Leu | Gly | Asn | 20 | 25 | 30 | |
| Gly | Ala | Leu | Leu | Val | Val | Val | Leu | Arg | Thr | Pro | Gly | Leu | Arg | Asp | Ala | 35 | 40 | 45 | |
| Leu | Tyr | Leu | Ala | His | Leu | Cys | Val | Val | Asp | Leu | Leu | Ala | Ala | Ala | Ser | 50 | 55 | 60 | |
| Ile | Met | Pro | Leu | Gly | Leu | Leu | Ala | Ala | Pro | Pro | Pro | Gly | Leu | Gly | Arg | 65 | 70 | 75 | 80 |
| Val | Arg | Leu | Gly | Pro | Ala | Pro | Cys | Arg | Ala | Ala | Arg | Phe | Leu | Ser | Ala | 85 | 90 | 95 | |
| Ala | Leu | Leu | Pro | Ala | Cys | Thr | Leu | Gly | Val | Ala | Ala | Leu | Gly | Leu | Ala | 100 | 105 | 110 | |
| Arg | Tyr | Arg | Leu | Ile | Val | His | Pro | Leu | Arg | Pro | Gly | Ser | Arg | Pro | Pro | 115 | 120 | 125 | |
| Pro | Val | Leu | Val | Leu | Thr | Ala | Val | Trp | Ala | Ala | Ala | Gly | Leu | Leu | Gly | 130 | 135 | 140 | |
| Ala | Leu | Ser | Leu | Leu | Gly | Pro | Pro | Pro | Ala | Pro | Pro | Pro | Ala | Pro | Ala | 145 | 150 | 155 | 160 |
| Arg | Cys | Ser | Val | Leu | Ala | Gly | Gly | Leu | Gly | Pro | Phe | Arg | Pro | Leu | Trp | 165 | 170 | 175 | |
| Ala | Leu | Leu | Ala | Phe | Ala | Leu | Pro | Ala | Leu | Leu | Leu | Leu | Gly | Ala | Tyr | 180 | 185 | 190 | |
| Gly | Gly | Ile | Phe | Val | Val | Ala | Arg | Arg | Ala | Ala | Leu | Arg | Pro | Pro | Arg | 195 | 200 | 205 | |
| Pro | Ala | Arg | Gly | Ser | Arg | Leu | Arg | Ser | Asp | Ser | Leu | Asp | Ser | Arg | Leu | 210 | 215 | 220 | |
| Ser | Ile | Leu | Pro | Pro | Leu | Arg | Pro | Arg | Leu | Pro | Gly | Gly | Lys | Ala | Ala | 225 | 230 | 235 | 240 |
| Leu | Ala | Pro | Ala | Leu | Ala | Val | Gly | Gln | Phe | Ala | Ala | Cys | Trp | Leu | Pro | | | | |

- 9 -

| | 245 | 250 | 255 |
|----|---|-----|-----|
| | Tyr Gly Cys Ala Cys Leu Ala Pro Ala Ala Arg Ala Ala Glu Ala Glu | | |
| | 260 | 265 | 270 |
| 5 | Ala Ala Val Thr Trp Val Ala Tyr Ser Ala Phe Ala Ala His Pro Phe | | |
| | 275 | 280 | 285 |
| | Leu Tyr Gly Leu Leu Gln Arg Pro Val Arg Leu Ala Leu Gly Arg Leu | | |
| | 290 | 295 | 300 |
| | Ser Arg Arg Ala Leu Pro Gly Pro Val Arg Ala Cys Thr Pro Gln Ala | | |
| | 305 | 310 | 315 |
| 10 | Trp His Pro Arg Ala Leu Leu Gln Cys Leu Gln Arg Pro Pro Glu Gly | | |
| | 325 | 330 | 335 |
| | Pro Ala Val Gly Pro Ser Glu Ala Pro Glu Gln Thr Pro Glu Leu Ala | | |
| | 340 | 345 | 350 |
| 15 | Gly Gly Arg Ser Pro Ala Tyr Gln Gly Pro Pro Glu Ser Ser Leu Ser | | |
| | 355 | 360 | 365 |

(8) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1008 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

| | | |
|----|---|-----|
| | ATGGAATCAT CTTTCTCATT TGGAGTGATC CTTGCTGTCC TGGCCTCCCT CATCATTGCT | 60 |
| 25 | ACTAACACAC TAGTGGCTGT GGCTGTGCTG CTGTTGATCC ACAAGAATGA TGGTGTCACT | 120 |
| | CTCTGCTTCA CCTTGAATCT GGCTGTGGCT GACACCTTGA TTGGTGTGGC CATCTCTGGC | 180 |
| | CTACTCACAG ACCAGCTCTC CAGCCCTTCT CGGCCCACAC AGAAGACCCT GTGCAGCCTG | 240 |
| | CGGATGGCAT TTGTCACTTC CTCCGCAGCT GCCTCTGTCC TCACGGTCAT GCTGATCACC | 300 |
| | TTTGACAGGT ACCTTGCCAT CAAGCAGCCC TTCCGCTACT TGAAGATCAT GAGTGGGTTC | 360 |
| 30 | GTGGCCGGGG CCTGCATTGC CGGGCTGTGG TTAGTGTCTT ACCTCATTGG CTTCTCTCCA | 420 |
| | CTCGGAATCC CCATGTTCCA GCAGACTGCC TACAAAGGGC AGTGCAGCTT CTTTGCTGTA | 480 |
| | TTTACCCTC ACTTCGTGCT GACCCTCTCC TGC GTTGGCT TCTTCCCAGC CATGCTCCTC | 540 |
| | TTTGTCTTCT TCTACTGCGA CATGCTCAAG ATTGCCTCCA TGCACAGCCA GCAGATTCGA | 600 |

- 10 -

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AAGATGGAAC ATGCAGGAGC CATGGCTGGA GGTTATCGAT CCCCACGGAC TCCCAGCGAC      660
TTCAAAGCTC TCCGTACTGT GTCTGTTCTC ATTGGGAGCT TTGCTCTATC CTGGACCCCC      720
TTCCTTATCA CTGGCATTGT GCAGGTGGCC TGCCAGGAGT GTCACCTCTA CCTAGTGCTG      780
GAACGGTACC TGTGGCTGCT CGGCGTGGGC AACTCCCTGC TCAACCCACT CATCTATGCC      840
5  TATTGGCAGA AGGAGGTGCG ACTGCAGCTC TACCACATGG CCCTAGGAGT GAAGAAGGTG      900
CTCACCTCAT TCCTCCTCTT TCTCTCGGCC AGGAATTGTG GCCCAGAGAG GCCCAGGGAA      960
AGTTCCTGTC ACATCGTCAC TATCTCCAGC TCAGAGTTTG ATGGCTAA                    1008

```

(9) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 335 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```

Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser
1           5           10           15

Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu
          20           25           30

20 Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala
          35           40           45

Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
          50           55           60

25 Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
          65           70           75           80

Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
          85           90           95

Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
          100          105          110

30 Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
          115          120          125

Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
          130          135          140

Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val

```

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 145 | | 150 | | 155 | | 160 | | | | | | | | | | |
| | Phe | His | Pro | His | Phe | Val | Leu | Thr | Leu | Ser | Cys | Val | Gly | Phe | Phe | Pro | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| 5 | Ala | Met | Leu | Leu | Phe | Val | Phe | Phe | Tyr | Cys | Asp | Met | Leu | Lys | Ile | Ala | |
| | | | | | 180 | | | | | 185 | | | | | 190 | | |
| | Ser | Met | His | Ser | Gln | Gln | Ile | Arg | Lys | Met | Glu | His | Ala | Gly | Ala | Met | |
| | | | | | 195 | | | | | 200 | | | | | 205 | | |
| | Ala | Gly | Gly | Tyr | Arg | Ser | Pro | Arg | Thr | Pro | Ser | Asp | Phe | Lys | Ala | Leu | |
| | | | | | 210 | | | | | 215 | | | | 220 | | | |
| 10 | Arg | Thr | Val | Ser | Val | Leu | Ile | Gly | Ser | Phe | Ala | Leu | Ser | Trp | Thr | Pro | |
| | | | | | 225 | | | | | 230 | | | | 235 | | | 240 |
| | Phe | Leu | Ile | Thr | Gly | Ile | Val | Gln | Val | Ala | Cys | Gln | Glu | Cys | His | Leu | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 15 | Tyr | Leu | Val | Leu | Glu | Arg | Tyr | Leu | Trp | Leu | Leu | Gly | Val | Gly | Asn | Ser | |
| | | | | | 260 | | | | | 265 | | | | | 270 | | |
| | Leu | Leu | Asn | Pro | Leu | Ile | Tyr | Ala | Tyr | Trp | Gln | Lys | Glu | Val | Arg | Leu | |
| | | | | | 275 | | | | | 280 | | | | 285 | | | |
| | Gln | Leu | Tyr | His | Met | Ala | Leu | Gly | Val | Lys | Lys | Val | Leu | Thr | Ser | Phe | |
| | | | | | 290 | | | | | 295 | | | | 300 | | | |
| 20 | Leu | Leu | Phe | Leu | Ser | Ala | Arg | Asn | Cys | Gly | Pro | Glu | Arg | Pro | Arg | Glu | |
| | | | | | 305 | | | | | 310 | | | | 315 | | | 320 |
| | Ser | Ser | Cys | His | Ile | Val | Thr | Ile | Ser | Ser | Ser | Glu | Phe | Asp | Gly | | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |

(10) INFORMATION FOR SEQ ID NO:9:

- 25 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1413 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

- 30 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

| | | | | | | |
|------------|------------|------------|------------|------------|------------|-----|
| ATGGACACTA | CCATGGAAGC | TGACCTGGGT | GCCACTGGCC | ACAGGCCCCG | CACAGAGCTT | 60 |
| GATGATGAGG | ACTCCTACCC | CCAAGGTGGC | TGGGACACGG | TCTTCCTGGT | GGCCCTGCTG | 120 |
| CTCCTTGGGC | TGCCAGCCAA | TGGGTTGATG | GCGTGGCTGG | CCGGCTCCCA | GGCCCGGCAT | 180 |
| GGAGCTGGCA | CGCGTCTGGC | GCTGCTCCTG | CTCAGCCTGG | CCCTCTCTGA | CTTCTTGTTT | 240 |

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CTGGCAGCAG CGGCCTTCCA GATCCTAGAG ATCCGGCATG GGGGACACTG GCCGCTGGGG 300
 ACAGCTGCCT GCCGCTTCTA CTACTTCCTA TGGGGCGTGT CCTACTCCTC CGGCCTCTTC 360
 CTGCTGGCCG CCCTCAGCCT CGACCGCTGC CTGCTGGCGC TGTGCCCACA CTGGTACCCT 420
 GGGCACC GCC CAGTCCGCCT GCCCCTCTGG GTCTGCGCCG GTGTCTGGGT GCTGGCCACA 480
 5 CTCTTCAGCG TGCCCTGGCT GGTCTTCCCC GAGGCTGCCG TCTGGTGGTA CGACCTGGTC 540
 ATCTGCCTGG ACTTCTGGGA CAGCGAGGAG CTGTGCTGA GGATGCTGGA GGTCTGGGG 600
 GGCTTCCTGC CTTTCCTCCT GCTGCTCGTC TGCCACGTGC TCACCCAGGC CACAGCCTGT 660
 CGCACCTGCC ACCGCCAACA GCAGCCCGCA GCCTGCCGGG GCTTCGCCCC TGTGGCCAGG 720
 ACCATTCTGT CAGCCTATGT GGTCTGAGG CTGCCCTACC AGCTGGCCCA GCTGCTCTAC 780
 10 CTGGCCTTCC TGTGGGACGT CTACTCTGGC TACCTGCTCT GGGAGGCCCT GGTCTACTCC 840
 GACTACCTGA TCCTACTCAA CAGCTGCCTC AGCCCCTTCC TCTGCCTCAT GGCCAGTGCC 900
 GACCTCCGGA CCCTGCTGCG CTCCGTGCTC TCGTCCTTCG CGGCAGCTCT CTGCGAGGAG 960
 CGGCCGGGCA GCTTCACGCC CACTGAGCCA CAGACCCAGC TAGATTCTGA GGGTCCAAC 1020
 CTGCCAGAGC CGATGGCAGA GGCCAGTCA CAGATGGATC CTGTGGCCCA GCCTCAGGTG 1080
 15 AACCCACAC TCCAGCCACG ATCGGATCCC ACAGCTCAGC CACAGCTGAA CCCTACGGCC 1140
 CAGCCACAGT CGGATCCCAC AGCCAGCCA CAGCTGAACC TCATGGCCCA GCCACAGTCA 1200
 GATTCTGTGG CCCAGCCACA GGCAGACACT AACGTCCAGA CCCCTGCACC TGCTGCCAGT 1260
 TCTGTGCCCA GTCCCTGTGA TGAAGCTTCC CCAACCCCAT CCTCGCATCC TACCCAGGG 1320
 GCCCTTGAGG ACCCAGCCAC ACCTCCTGCC TCTGAAGGAG AAAGCCCCAG CAGCACCCCG 1380
 20 CCAGAGGCGG CCCCGGGCGC AGGCCCCACG TGA 1413

(11) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 468 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

30 Met Asp Thr Thr Met Glu Ala Asp Leu Gly Ala Thr Gly His Arg Pro
 1 5 10 15

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Arg | Thr | Glu | Leu | Asp | Asp | Glu | Asp | Ser | Tyr | Pro | Gln | Gly | Gly | Trp | Asp | |
| | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | Thr | Val | Phe | Leu | Val | Ala | Leu | Leu | Leu | Leu | Gly | Leu | Pro | Ala | Asn | Gly | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| 5 | Leu | Met | Ala | Trp | Leu | Ala | Gly | Ser | Gln | Ala | Arg | His | Gly | Ala | Gly | Thr | |
| | | 50 | | | | | 55 | | | | | 60 | | | | | |
| | Arg | Leu | Ala | Leu | Leu | Leu | Leu | Ser | Leu | Ala | Leu | Ser | Asp | Phe | Leu | Phe | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| 10 | Leu | Ala | Ala | Ala | Ala | Phe | Gln | Ile | Leu | Glu | Ile | Arg | His | Gly | Gly | His | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| | Trp | Pro | Leu | Gly | Thr | Ala | Ala | Cys | Arg | Phe | Tyr | Tyr | Phe | Leu | Trp | Gly | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| | Val | Ser | Tyr | Ser | Ser | Gly | Leu | Phe | Leu | Leu | Ala | Ala | Leu | Ser | Leu | Asp | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| 15 | Arg | Cys | Leu | Leu | Ala | Leu | Cys | Pro | His | Trp | Tyr | Pro | Gly | His | Arg | Pro | |
| | | 130 | | | | | 135 | | | | | | 140 | | | | |
| | Val | Arg | Leu | Pro | Leu | Trp | Val | Cys | Ala | Gly | Val | Trp | Val | Leu | Ala | Thr | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| 20 | Leu | Phe | Ser | Val | Pro | Trp | Leu | Val | Phe | Pro | Glu | Ala | Ala | Val | Trp | Trp | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| | Tyr | Asp | Leu | Val | Ile | Cys | Leu | Asp | Phe | Trp | Asp | Ser | Glu | Glu | Leu | Ser | |
| | | | | 180 | | | | | | 185 | | | | 190 | | | |
| | Leu | Arg | Met | Leu | Glu | Val | Leu | Gly | Gly | Phe | Leu | Pro | Phe | Leu | Leu | Leu | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| 25 | Leu | Val | Cys | His | Val | Leu | Thr | Gln | Ala | Thr | Arg | Thr | Cys | His | Arg | Gln | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | Gln | Gln | Pro | Ala | Ala | Cys | Arg | Gly | Phe | Ala | Arg | Val | Ala | Arg | Thr | Ile | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| 30 | Leu | Ser | Ala | Tyr | Val | Val | Leu | Arg | Leu | Pro | Tyr | Gln | Leu | Ala | Gln | Leu | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| | Leu | Tyr | Leu | Ala | Phe | Leu | Trp | Asp | Val | Tyr | Ser | Gly | Tyr | Leu | Leu | Trp | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Glu | Ala | Leu | Val | Tyr | Ser | Asp | Tyr | Leu | Ile | Leu | Leu | Asn | Ser | Cys | Leu | |
| | | | | 275 | | | | 280 | | | | | 285 | | | | |
| 35 | Ser | Pro | Phe | Leu | Cys | Leu | Met | Ala | Ser | Ala | Asp | Leu | Arg | Thr | Leu | Leu | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | Arg | Ser | Val | Leu | Ser | Ser | Phe | Ala | Ala | Ala | Leu | Cys | Glu | Glu | Arg | Pro | |

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| | | | | | | | |
|----|---|-------------------------|-------------------------|-----|-----|--|-----|
| | 305 | | 310 | | 315 | | 320 |
| | Gly Ser Phe Thr | Pro Thr Glu Pro Gln Thr | Gln Leu Asp Ser Glu Gly | | | | |
| | | 325 | 330 | 335 | | | |
| 5 | Pro Thr Leu Pro Glu Pro Met Ala Glu Ala Gln Ser Gln Met Asp Pro | | | | | | |
| | | 340 | 345 | 350 | | | |
| | Val Ala Gln Pro Gln Val Asn Pro Thr Leu Gln Pro Arg Ser Asp Pro | | | | | | |
| | | 355 | 360 | 365 | | | |
| | Thr Ala Gln Pro Gln Leu Asn Pro Thr Ala Gln Pro Gln Ser Asp Pro | | | | | | |
| | | 370 | 375 | 380 | | | |
| 10 | Thr Ala Gln Pro Gln Leu Asn Leu Met Ala Gln Pro Gln Ser Asp Ser | | | | | | |
| | | 385 | 390 | 395 | 400 | | |
| | Val Ala Gln Pro Gln Ala Asp Thr Asn Val Gln Thr Pro Ala Pro Ala | | | | | | |
| | | 405 | 410 | 415 | | | |
| 15 | Ala Ser Ser Val Pro Ser Pro Cys Asp Glu Ala Ser Pro Thr Pro Ser | | | | | | |
| | | 420 | 425 | 430 | | | |
| | Ser His Pro Thr Pro Gly Ala Leu Glu Asp Pro Ala Thr Pro Pro Ala | | | | | | |
| | | 435 | 440 | 445 | | | |
| | Ser Glu Gly Glu Ser Pro Ser Ser Thr Pro Pro Glu Ala Ala Pro Gly | | | | | | |
| | | 450 | 455 | 460 | | | |
| 20 | Ala Gly Pro Thr | | | | | | |
| | 465 | | | | | | |

(12) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1248 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

| | | |
|----|---|-----|
| 30 | ATGTCAGGGA TGGAAAACT TCAGAATGCT TCCTGGATCT ACCAGCAGAA ACTAGAAGAT | 60 |
| | CCATTCCAGA AACACCTGAA CAGCACCGAG GAGTATCTGG CCTTCCTCTG CGGACCTCGG | 120 |
| | CGCAGCCACT TCTTCCTCCC CGTGTCTGTG GTGTATGTGC CAATTTTGT GGTGGGGGTC | 180 |
| | ATTGGCAATG TCCTGGTGTG CCTGGTGATT CTGCAGCACC AGGCTATGAA GACGCCCACC | 240 |
| | AACTACTACC TCTTCAGCCT GCGGTCTCT GACCTCCTGG TCCTGCTCCT TGGAAATGCC | 300 |

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CTGGAGGTCT ATGAGATGTG GCGCAACTAC CCTTTCTTGT TCGGGCCCCGT GGGCTGCTAC      360
TTCAAGACGG CCCTCTTTGA GACCGTGTGC TTCGCCTCCA TCCTCAGCAT CACCACCGTC      420
AGCGTGGAGC GCTACGTGGC CATCCTACAC CCGTTCCGCG CCAAAGTGA GAGCACCCGG      480
CGCCGGGCCC TCAGGATCCT CGGCATCGTC TGGGGCTTCT CCGTGCTCTT CTCCCTGCCC      540
5 AACACCAGCA TCCATGGCAT CAAGTTCCAC TACTTCCCCA ATGGGTCCCT GGTCCCAGGT      600
TCGGCCACCT GTACGGTCAT CAAGCCCATG TGGATCTACA ATTTTCATCAT CCAGGTCACC      660
TCCTTCCTAT TCTACCTCCT CCCCATGACT GTCATCAGTG TCCTCTACTA CCTCATGGCA      720
CTCAGACTAA AGAAAGACAA ATCTCTTGAG GCAGATGAAG GGAATGCAA TATTCAAAGA      780
CCCTGCAGAA AATCAGTCAA CAAGATGCTG TTTGTCTTGG TCTTAGTGTT TGCTATCTGT      840
10 TGGGCCCCGT TCCACATTGA CCGACTCTTC TTCAGCTTTG TGGAGGAGTG GAGTGAATCC      900
CTGGCTGCTG TGTTC AACCT CGTCCATGTG GTGTCAGGTG TCTTCTTCTA CCTGAGCTCA      960
GCTGTCAACC CCATTATCTA TAACCTACTG TCTCGCCGCT TCCAGGCAGC ATTCCAGAAT     1020
GTGATCTCTT CTTTCCACAA ACAGTGGCAC TCCCAGCATG ACCCACAGTT GCCACCTGCC     1080
CAGCGGAACA TCTTCTTGAC AGAATGCCAC TTTGTGGAGC TGACCGAAGA TATAGGTCCC     1140
15 CAATTCCCAT GTCAGTCATC CATGCACAAC TCTCACCTCC CAACAGCCCT CTCTAGTGAA     1200
CAGATGTCAA GAACAAACTA TCAAAGCTTC CACTTTAACA AAACCTGA                     1248

```

(13) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 415 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```

25 Met Ser Gly Met Glu Lys Leu Gln Asn Ala Ser Trp Ile Tyr Gln Gln
   1           5           10           15

   Lys Leu Glu Asp Pro Phe Gln Lys His Leu Asn Ser Thr Glu Glu Tyr
      20           25           30

   Leu Ala Phe Leu Cys Gly Pro Arg Arg Ser His Phe Phe Leu Pro Val
   35           40           45

   Ser Val Val Tyr Val Pro Ile Phe Val Val Gly Val Ile Gly Asn Val

```

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| | 50 | | | 55 | | | 60 | | | | | | | | | |
|----|------------|------------|------------|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Leu 65 | Val | Cys | Leu | Val | Ile 70 | Leu | Gln | His | Gln | Ala 75 | Met | Lys | Thr | Pro | Thr 80 |
| 5 | Asn | Tyr | Tyr | Leu | Phe 85 | Ser | Leu | Ala | Val | Ser 90 | Asp | Leu | Leu | Val | Leu 95 | Leu |
| | Leu | Gly | Met | Pro | Leu | Glu | Val | Tyr | Glu 105 | Met | Trp | Arg | Asn | Tyr 110 | Pro | Phe |
| | Leu | Phe | Gly 115 | Pro | Val | Gly | Cys | Tyr 120 | Phe | Lys | Thr | Ala | Leu 125 | Phe | Glu | Thr |
| 10 | Val | Cys 130 | Phe | Ala | Ser | Ile | Leu 135 | Ser | Ile | Thr | Thr | Val 140 | Ser | Val | Glu | Arg |
| | Tyr 145 | Val | Ala | Ile | Leu | His 150 | Pro | Phe | Arg | Ala | Lys 155 | Leu | Gln | Ser | Thr | Arg 160 |
| 15 | Arg | Arg | Ala | Leu | Arg 165 | Ile | Leu | Gly | Ile | Val 170 | Trp | Gly | Phe | Ser | Val 175 | Leu |
| | Phe | Ser | Leu | Pro | Asn 180 | Thr | Ser | Ile | His 185 | Gly | Ile | Lys | Phe | His 190 | Tyr | Phe |
| | Pro | Asn | Gly 195 | Ser | Leu | Val | Pro | Gly 200 | Ser | Ala | Thr | Cys | Thr 205 | Val | Ile | Lys |
| 20 | Pro | Met 210 | Trp | Ile | Tyr | Asn | Phe 215 | Ile | Ile | Gln | Val | Thr 220 | Ser | Phe | Leu | Phe |
| | Tyr 225 | Leu | Leu | Pro | Met | Thr 230 | Val | Ile | Ser | Val | Leu 235 | Tyr | Tyr | Leu | Met | Ala 240 |
| 25 | Leu | Arg | Leu | Lys | Lys 245 | Asp | Lys | Ser | Leu | Glu 250 | Ala | Asp | Glu | Gly | Asn 255 | Ala |
| | Asn | Ile | Gln | Arg | Pro | Cys | Arg | Lys | Ser 265 | Val | Asn | Lys | Met | Leu 270 | Phe | Val |
| | Leu | Val | Leu | Val | Phe | Ala | Ile | Cys 280 | Trp | Ala | Pro | Phe | His 285 | Ile | Asp | Arg |
| 30 | Leu | Phe 290 | Phe | Ser | Phe | Val | Glu 295 | Glu | Trp | Ser | Glu | Ser 300 | Leu | Ala | Ala | Val |
| | Phe 305 | Asn | Leu | Val | His | Val | Val | Ser | Gly | Val | Phe 315 | Phe | Tyr | Leu | Ser | Ser 320 |
| 35 | Ala | Val | Asn | Pro | Ile 325 | Ile | Tyr | Asn | Leu | Leu 330 | Ser | Arg | Arg | Phe | Gln 335 | Ala |
| | Ala | Phe | Gln | Asn | Val | Ile | Ser | Ser | Phe 345 | His | Lys | Gln | Trp | His 350 | Ser | Gln |

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His Asp Pro Gln Leu Pro Pro Ala Gln Arg Asn Ile Phe Leu Thr Glu
355 360 365

Cys His Phe Val Glu Leu Thr Glu Asp Ile Gly Pro Gln Phe Pro Cys
370 375 380

5 Gln Ser Ser Met His Asn Ser His Leu Pro Thr Ala Leu Ser Ser Glu
385 390 395 400

Gln Met Ser Arg Thr Asn Tyr Gln Ser Phe His Phe Asn Lys Thr
405 410 415

(14) INFORMATION FOR SEQ ID NO:13:

- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1173 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 15 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

| | | | | | | |
|---------------|------------|-------------|------------|------------|------------|-----|
| ATGCCAGATA | CTAATAGCAC | AATCAATTTA | TCACTAAGCA | CTCGTGTTAC | TTTAGCATTT | 60 |
| TTTATGTCCT | TAGTAGCTTT | TGCTATAATG | CTAGGAAATG | CTTGGTCAT | TTTAGCTTTT | 120 |
| GTGGTGACA | AAAACCTTAG | ACATCGAAGT | AGTTATTTTT | TTCTTAACTT | GGCCATCTCT | 180 |
| 20 GACTTCTTTG | TGGGTGTGAT | CTCCATTCCT | TTGTACATCC | CTCACACGCT | GTTCGAATGG | 240 |
| GATTTTGGA | AGGAAATCTG | TGTATTTTGG | CTCACTACTG | ACTATCTGTT | ATGTACAGCA | 300 |
| TCTGTATATA | ACATTGTCCT | CATCAGCTAT | GATCGATACC | TGTCAGTCTC | AAATGCTGTG | 360 |
| TCTTATAGAA | CTCAACATAC | TGGGGTCTTG | AAGATTGTTA | CTCTGATGGT | GGCCGTTTGG | 420 |
| GTGCTGGCCT | TCTTAGTGAA | TGGGCCAATG | ATTCTAGTTT | CAGAGTCTTG | GAAGGATGAA | 480 |
| 25 GGTAGTGAAT | GTGAACCTGG | ATTTTTTTTCG | GAATGGTACA | TCCTTGCCAT | CACATCATTC | 540 |
| TTGGAATTCG | TGATCCCAGT | CATCTTAGTC | GCTTATTTCA | ACATGAATAT | TTATTGGAGC | 600 |
| CTGTGGAAGC | GTGATCATCT | CAGTAGGTGC | CAAAGCCATC | CTGGACTGAC | TGCTGTCTCT | 660 |
| TCCAACATCT | GTGGACACTC | ATTCAGAGGT | AGACTATCTT | CAAGGAGATC | TCTTTCTGCA | 720 |
| TCGACAGAAG | TTCCTGCATC | CTTTCATTCA | GAGAGACAGA | GGAGAAAGAG | TAGTCTCATG | 780 |
| 30 TTTTCCTCAA | GAACCAAGAT | GAATAGCAAT | ACAATTGCTT | CCAAAATGGG | TTCTTCTCC | 840 |
| CAATCAGATT | CTGTAGCTCT | TCACCAAAGG | GAACATGTTG | AACTGCTTAG | AGCCAGGAGA | 900 |

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TTAGCCAAGT CACTGGCCAT TCTCTTAGGG GTTTTGTGCTG TTTGCTGGGC TCCATATTCT 960
 CTGTTACAAA TTGTCCTTTC ATTTTATTCC TCAGCAACAG GTCCTAAATC AGTTTGGTAT 1020
 AGAATTGCAT TTTGGCTTCA GTGGTTCAAT TCCTTTGTCA ATCCTCTTTT GTATCCATTG 1080
 TGTCACAAGC GCTTTCAAAA GGCTTTCTTG AAAATATTTT GTATAAAAAA GCAACCTCTA 1140
 5 CCATCACAAC ACAGTCGGTC AGTATCTTCT TAA 1173

(15) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 390 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Pro Asp Thr Asn Ser Thr Ile Asn Leu Ser Leu Ser Thr Arg Val
 1 5 10 15
 Thr Leu Ala Phe Phe Met Ser Leu Val Ala Phe Ala Ile Met Leu Gly
 20 25 30
 Asn Ala Leu Val Ile Leu Ala Phe Val Val Asp Lys Asn Leu Arg His
 35 40 45
 Arg Ser Ser Tyr Phe Phe Leu Asn Leu Ala Ile Ser Asp Phe Phe Val
 50 55 60
 Gly Val Ile Ser Ile Pro Leu Tyr Ile Pro His Thr Leu Phe Glu Trp
 65 70 75 80
 Asp Phe Gly Lys Glu Ile Cys Val Phe Trp Leu Thr Thr Asp Tyr Leu
 85 90 95
 Leu Cys Thr Ala Ser Val Tyr Asn Ile Val Leu Ile Ser Tyr Asp Arg
 100 105 110
 Tyr Leu Ser Val Ser Asn Ala Val Ser Tyr Arg Thr Gln His Thr Gly
 115 120 125
 Val Leu Lys Ile Val Thr Leu Met Val Ala Val Trp Val Leu Ala Phe
 130 135 140
 Leu Val Asn Gly Pro Met Ile Leu Val Ser Glu Ser Trp Lys Asp Glu
 145 150 155 160
 Gly Ser Glu Cys Glu Pro Gly Phe Phe Ser Glu Trp Tyr Ile Leu Ala
 165 170 175

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Ile | Thr | Ser | Phe | Leu | Glu | Phe | Val | Ile | Pro | Val | Ile | Leu | Val | Ala | Tyr | |
| | | | | 180 | | | | | 185 | | | | 190 | | | | |
| | Phe | Asn | Met | Asn | Ile | Tyr | Trp | Ser | Leu | Trp | Lys | Arg | Asp | His | Leu | Ser | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| 5 | Arg | Cys | Gln | Ser | His | Pro | Gly | Leu | Thr | Ala | Val | Ser | Ser | Asn | Ile | Cys | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | Gly | His | Ser | Phe | Arg | Gly | Arg | Leu | Ser | Ser | Arg | Arg | Ser | Leu | Ser | Ala | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Ser | Thr | Glu | Val | Pro | Ala | Ser | Phe | His | Ser | Glu | Arg | Gln | Arg | Arg | Lys | |
| 10 | | | | | 245 | | | | | 250 | | | | | 255 | | |
| | Ser | Ser | Leu | Met | Phe | Ser | Ser | Arg | Thr | Lys | Met | Asn | Ser | Asn | Thr | Ile | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Ala | Ser | Lys | Met | Gly | Ser | Phe | Ser | Gln | Ser | Asp | Ser | Val | Ala | Leu | His | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| 15 | Gln | Arg | Glu | His | Val | Glu | Leu | Leu | Arg | Ala | Arg | Arg | Leu | Ala | Lys | Ser | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | Leu | Ala | Ile | Leu | Leu | Gly | Val | Phe | Ala | Val | Cys | Trp | Ala | Pro | Tyr | Ser | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Leu | Phe | Thr | Ile | Val | Leu | Ser | Phe | Tyr | Ser | Ser | Ala | Thr | Gly | Pro | Lys | |
| 20 | | | | | 325 | | | | | 330 | | | | | 335 | | |
| | Ser | Val | Trp | Tyr | Arg | Ile | Ala | Phe | Trp | Leu | Gln | Trp | Phe | Asn | Ser | Phe | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| | Val | Asn | Pro | Leu | Leu | Tyr | Pro | Leu | Cys | His | Lys | Arg | Phe | Gln | Lys | Ala | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| 25 | Phe | Leu | Lys | Ile | Phe | Cys | Ile | Lys | Lys | Gln | Pro | Leu | Pro | Ser | Gln | His | |
| | | 370 | | | | | 375 | | | | | 380 | | | | | |
| | Ser | Arg | Ser | Val | Ser | Ser | | | | | | | | | | | |
| | 385 | | | | | 390 | | | | | | | | | | | |

(16) INFORMATION FOR SEQ ID NO:15:

- 30 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 35 (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

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GGAAAGCTTA ACGATCCCCA GGAGCAACAT

30

(17) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 31 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iv) ANTI-SENSE: YES

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CTGGGATCCT ACGAGAGCAT TTTTCACACA G
 31

.(18) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1128 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

| | | | | | | |
|---------------|------------|------------|------------|------------|-------------|-----|
| ATGGCGAACG | CGAGCGAGCC | GGGTGGCAGC | GGCGGCGGCG | AGGCGGCCGC | CCTGGGCCTC | 60 |
| AAGCTGGCCA | CGCTCAGCCT | GCTGCTGTGC | GTGAGCCTAG | CGGGCAACGT | GCTGTTTCGCG | 120 |
| CTGCTGATCG | TGCGGGAGCG | CAGCCTGCAC | CGCGCCCCGT | ACTACCTGCT | GCTCGACCTG | 180 |
| TGCCTGGCCG | ACGGGCTGCG | CGCGCTCGCC | TGCCTCCCGG | CCGTCATGCT | GGCGGCGCGG | 240 |
| 25 CGTGCGGCGG | CCGCGGCGGG | GGCGCCGCCG | GGCGCGCTGG | GCTGCAAGCT | GCTCGCCTTC | 300 |
| CTGGCCGCGC | TCTTCTGCTT | CCACGCCGCC | TTCCTGCTGC | TGGGCGTGGG | CGTCACCCGC | 360 |
| TACCTGGCCA | TCGCGCACCA | CCGCTTCTAT | GCAGAGCGCC | TGGCCGGCTG | GCCGTGCGCC | 420 |
| GCCATGCTGG | TGTGCGCCGC | CTGGGCGCTG | GCGCTGGCCG | CGGCCTTCCC | GCCAGTGCTG | 480 |
| GACGGCGGTG | GCGACGACGA | GGACGCGCCG | TGCGCCCTGG | AGCAGCGGCC | CGACGGCGCC | 540 |
| 30 CCCGGCGCGC | TGGGCTTCCT | GCTGCTGCTG | GCCGTGGTGG | TGGGCGCCAC | GCACCTCGTC | 600 |
| TACCTCCGCC | TGCTCTTCTT | CATCCACGAC | CGCCGCAAGA | TGCGGCCCGC | GCGCCTGGTG | 660 |

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CCCCCGTCA GCCACGACTG GACCTTCCAC GGCCCGGGCG CCACCGGCCA GGCGGCCGCC      720
AACTGGACGG CGGGCTTCGG CCGCGGGGCC ACGCCGCCCC CGCTTGTGGG CATCCGGCCC      780
GCAGGGCCGG GCCGCGGCGC GCGCCGCCTC CTCGTGCTGG AAGAATTCAA GACGGAGAAG      840
AGGCTGTGCA AGATGTTCTA CGCCGTCACG CTGCTCTTCC TGCTCCTCTG GGGGCCCTAC      900
5  GTCGTGGCCA GCTACCTGCG GGTCCCTGGTG CGGCCCCGGCG CCGTCCCCCA GGCCTACCTG      960
ACGGCCTCCG TGTGGCTGAC CTTCGCGCAG GCCGGCATCA ACCCCGTCGT GTGCTTCCTC     1020
TTCAACAGGG AGCTGAGGGA CTGCTTCAGG GCCCAGTTCC CCTGCTGCCA GAGCCCCCGG     1080
ACCACCCAGG CGACCCATCC CTGCGACCTG AAAGGCATTG GTTTATGA                     1128

```

(19) INFORMATION FOR SEQ ID NO:18:

- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 375 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```

Met Ala Asn Ala Ser Glu Pro Gly Gly Ser Gly Gly Gly Glu Ala Ala
1           5           10           15

Ala Leu Gly Leu Lys Leu Ala Thr Leu Ser Leu Leu Leu Cys Val Ser
20          20          25          30

Leu Ala Gly Asn Val Leu Phe Ala Leu Leu Ile Val Arg Glu Arg Ser
35          40          45

Leu His Arg Ala Pro Tyr Tyr Leu Leu Leu Asp Leu Cys Leu Ala Asp
50          55          60

25 Gly Leu Arg Ala Leu Ala Cys Leu Pro Ala Val Met Leu Ala Ala Arg
65          70          75          80

Arg Ala Ala Ala Ala Ala Gly Ala Pro Pro Gly Ala Leu Gly Cys Lys
85          90          95

30 Leu Leu Ala Phe Leu Ala Ala Leu Phe Cys Phe His Ala Ala Phe Leu
100         105         110

Leu Leu Gly Val Gly Val Thr Arg Tyr Leu Ala Ile Ala His His Arg
115         120         125

Phe Tyr Ala Glu Arg Leu Ala Gly Trp Pro Cys Ala Ala Met Leu Val
130         135         140

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Cys | Ala | Ala | Trp | Ala | Leu | Ala | Leu | Ala | Ala | Ala | Phe | Pro | Pro | Val | Leu | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Asp | Gly | Gly | Gly | Asp | Asp | Glu | Asp | Ala | Pro | Cys | Ala | Leu | Glu | Gln | Arg | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| 5 | Pro | Asp | Gly | Ala | Pro | Gly | Ala | Leu | Gly | Phe | Leu | Leu | Leu | Leu | Ala | Val | |
| | | | | | 180 | | | | 185 | | | | | | 190 | | |
| | Val | Val | Gly | Ala | Thr | His | Leu | Val | Tyr | Leu | Arg | Leu | Leu | Phe | Phe | Ile | |
| | | | | | 195 | | | | 200 | | | | | 205 | | | |
| 10 | His | Asp | Arg | Arg | Lys | Met | Arg | Pro | Ala | Arg | Leu | Val | Pro | Ala | Val | Ser | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | His | Asp | Trp | Thr | Phe | His | Gly | Pro | Gly | Ala | Thr | Gly | Gln | Ala | Ala | Ala | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Asn | Trp | Thr | Ala | Gly | Phe | Gly | Arg | Gly | Pro | Thr | Pro | Pro | Ala | Leu | Val | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 15 | Gly | Ile | Arg | Pro | Ala | Gly | Pro | Gly | Arg | Gly | Ala | Arg | Arg | Leu | Leu | Val | |
| | | | | | 260 | | | | 265 | | | | | 270 | | | |
| | Leu | Glu | Glu | Phe | Lys | Thr | Glu | Lys | Arg | Leu | Cys | Lys | Met | Phe | Tyr | Ala | |
| | | | | | 275 | | | | 280 | | | | 285 | | | | |
| 20 | Val | Thr | Leu | Leu | Phe | Leu | Leu | Leu | Trp | Gly | Pro | Tyr | Val | Val | Ala | Ser | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | Tyr | Leu | Arg | Val | Leu | Val | Arg | Pro | Gly | Ala | Val | Pro | Gln | Ala | Tyr | Leu | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Thr | Ala | Ser | Val | Trp | Leu | Thr | Phe | Ala | Gln | Ala | Gly | Ile | Asn | Pro | Val | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| 25 | Val | Cys | Phe | Leu | Phe | Asn | Arg | Glu | Leu | Arg | Asp | Cys | Phe | Arg | Ala | Gln | |
| | | | | | 340 | | | | 345 | | | | | 350 | | | |
| | Phe | Pro | Cys | Cys | Gln | Ser | Pro | Arg | Thr | Thr | Gln | Ala | Thr | His | Pro | Cys | |
| | | | | | 355 | | | | 360 | | | | | 365 | | | |
| 30 | Asp | Leu | Lys | Gly | Ile | Gly | Leu | | | | | | | | | | |
| | | 370 | | | | | 375 | | | | | | | | | | |

(20) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1002 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```

ATGAACACCA CAGTGATGCA AGGCTTCAAC AGATCTGAGC GGTGCCCCAG AGACACTCGG      60
ATAGTACAGC TGGTATTCCC AGCCCTCTAC ACAGTGGTTT TCTTGACCGG CATCCTGCTG      120
AATACTTTGG CTCTGTGGGT GTTTGTTCAC ATCCCCAGCT CCTCCACCTT CATCATCTAC      180
5  CTCAAAAACA CTTTGGTGGC CGACTTGATA ATGACACTCA TGCTTCCTTT CAAAATCCTC      240
TCTGACTCAC ACCTGGCACC CTGGCAGCTC AGAGCTTTTG TGTGTCGTTT TTCTTCGGTG      300
ATATTTTATG AGACCATGTA TGTGGGCATC GTGCTGTTAG GGCTCATAGC CTTTGACAGA      360
TTCCTCAAGA TCATCAGACC TTTGAGAAAT ATTTTCTAA AAAAACCTGT TTTTGCAAAA      420
ACGGTCTCAA TCTTCATCTG GTTCTTTTTG TTCTTCATCT CCCTGCCAAA TACGATCTTG      480
10 AGCAACAAGG AAGCAACACC ATCGTCTGTG AAAAAGTGTG CTTCTTAAA GGGGCCTCTG      540
GGGCTGAAAT GGCATCAAAT GGTAAATAAC ATATGCCAGT TTATTTTCTG GACTGTTTTT      600
ATCCTAATGC TTGTGTTTTA TGTGGTTATT GCAAAAAAAG TATATGATTC TTATAGAAAG      660
TCCAAAAGTA AGGACAGAAA AAACAACAAA AAGCTGGAAG GCAAAGTATT TGTGTGCGTG      720
GCTGTCTTCT TTGTGTGTTT TGCTCCATTT CATTTTGCCA GAGTTCCATA TACTCACAGT      780
15 CAAACCAACA ATAAGACTGA CTGTAGACTG CAAATCAAC TGTTTATTGC TAAAGAAACA      840
ACTCTCTTTT TGGCAGCAAC TAACATTTGT ATGGATCCCT TAATATACAT ATTCTTATGT      900
AAAAAATTCA CAGAAAAGCT ACCATGTATG CAAGGGAGAA AGACCACAGC ATCAAGCCAA      960
GAAAATCATA GCAGTCAGAC AGACAACATA ACCTTAGGCT GA                                1002

```

(21) INFORMATION FOR SEQ ID NO:20:

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 333 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant
- 25 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```

Met Asn Thr Thr Val Met Gln Gly Phe Asn Arg Ser Glu Arg Cys Pro
 1              5              10              15

Arg Asp Thr Arg Ile Val Gln Leu Val Phe Pro Ala Leu Tyr Thr Val
30              20              25              30

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Val | Phe | Leu | Thr | Gly | Ile | Leu | Leu | Asn | Thr | Leu | Ala | Leu | Trp | Val | Phe | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| | Val | His | Ile | Pro | Ser | Ser | Ser | Thr | Phe | Ile | Ile | Tyr | Leu | Lys | Asn | Thr | |
| | | 50 | | | | | 55 | | | | | 60 | | | | | |
| 5 | Leu | Val | Ala | Asp | Leu | Ile | Met | Thr | Leu | Met | Leu | Pro | Phe | Lys | Ile | Leu | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| | Ser | Asp | Ser | His | Leu | Ala | Pro | Trp | Gln | Leu | Arg | Ala | Phe | Val | Cys | Arg | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| 10 | Phe | Ser | Ser | Val | Ile | Phe | Tyr | Glu | Thr | Met | Tyr | Val | Gly | Ile | Val | Leu | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| | Leu | Gly | Leu | Ile | Ala | Phe | Asp | Arg | Phe | Leu | Lys | Ile | Ile | Arg | Pro | Leu | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | Arg | Asn | Ile | Phe | Leu | Lys | Lys | Pro | Val | Phe | Ala | Lys | Thr | Val | Ser | Ile | |
| | | 130 | | | | | 135 | | | | | | 140 | | | | |
| 15 | Phe | Ile | Trp | Phe | Phe | Leu | Phe | Phe | Ile | Ser | Leu | Pro | Asn | Thr | Ile | Leu | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Ser | Asn | Lys | Glu | Ala | Thr | Pro | Ser | Ser | Val | Lys | Lys | Cys | Ala | Ser | Leu | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| 20 | Lys | Gly | Pro | Leu | Gly | Leu | Lys | Trp | His | Gln | Met | Val | Asn | Asn | Ile | Cys | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| | Gln | Phe | Ile | Phe | Trp | Thr | Val | Phe | Ile | Leu | Met | Leu | Val | Phe | Tyr | Val | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| | Val | Ile | Ala | Lys | Lys | Val | Tyr | Asp | Ser | Tyr | Arg | Lys | Ser | Lys | Ser | Lys | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| 25 | Asp | Arg | Lys | Asn | Asn | Lys | Lys | Leu | Glu | Gly | Lys | Val | Phe | Val | Val | Val | |
| | 225 | | | | 230 | | | | | | 235 | | | | | 240 | |
| | Ala | Val | Phe | Phe | Val | Cys | Phe | Ala | Pro | Phe | His | Phe | Ala | Arg | Val | Pro | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 30 | Tyr | Thr | His | Ser | Gln | Thr | Asn | Asn | Lys | Thr | Asp | Cys | Arg | Leu | Gln | Asn | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Gln | Leu | Phe | Ile | Ala | Lys | Glu | Thr | Thr | Leu | Phe | Leu | Ala | Ala | Thr | Asn | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| | Ile | Cys | Met | Asp | Pro | Leu | Ile | Tyr | Ile | Phe | Leu | Cys | Lys | Lys | Phe | Thr | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| 35 | Glu | Lys | Leu | Pro | Cys | Met | Gln | Gly | Arg | Lys | Thr | Thr | Ala | Ser | Ser | Gln | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Glu | Asn | His | Ser | Ser | Gln | Thr | Asp | Asn | Ile | Thr | Leu | Gly | | | | |

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325

330

(22) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 1122 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

10 ATGGCCAACA CTACCGGAGA GCCTGAGGAG GTGAGCGGCG CTCTGTCCCC ACCGTCCGCA 60
TCAGCTTATG TGAAGCTGGT ACTGCTGGGA CTGATTATGT GCGTGAGCCT GGCGGGTAAC 120
GCCATCTTGT CCCTGCTGGT GCTCAAGGAG CGTGCCCTGC ACAAGGCTCC TTACTACTTC 180
CTGCTGGACC TGTGCCTGGC CGATGGCATA CGCTCTGCCG TCTGCTTCCC CTTTGTGCTG 240
GCTTCTGTGC GCCACGGCTC TTCATGGACC TTCAGTGCAC TCAGCTGCAA GATTGTGGCC 300
15 TTTATGGCCG TGCTCTTTTG CTTCCATGCG GCCTTCATGC TGTTCTGCAT CAGCGTCACC 360
CGCTACATGG CCATCGCCCA CCACCGCTTC TACGCCAAGC GCATGACACT CTGGACATGC 420
GCGGCTGTCA TCTGCATGGC CTGGACCCTG TCTGTGGCCA TGGCCTTCCC ACCTGTCTTT 480
GACGTGGGCA CCTACAAGTT TATTCGGGAG GAGGACCAGT GCATCTTTGA GCATCGCTAC 540
TTCAAGGCCA ATGACACGCT GGGCTTCATG CTTATGTTGG CTGTGCTCAT GGCAGCTACC 600
20 CATGCTGTCT ACGGCAAGCT GTCCTCTTC GAGTATCGTC ACCGCAAGAT GAAGCCAGTG 660
CAGATGGTGC CAGCCATCAG CCAGAACTGG ACATTCCATG GTCCCGGGGC CACCGGCCAG 720
GCTGCTGCCA ACTGGATCGC CGGCTTTGGC CGTGGGCCCCA TGCCACCAAC CCTGCTGGGT 780
ATCCGGCAGA ATGGGCATGC AGCCAGCCGG CGGCTACTGG GCATGGACGA GGTCAAGGGT 840
GAAAAGCAGC TGGGCCGCAT GTTCTACGCG ATCACACTGC TCTTTCTGCT CCTCTGGTCA 900
25 CCCTACATCG TGGCCTGCTA CTGGCGAGTG TTTGTGAAAG CCTGTGCTGT GCCCCACCGC 960
TACCTGGCCA CTGCTGTTTG GATGAGCTTC GCCCAGGCTG CCGTCAACCC AATTGTCTGC 1020
TTCCTGCTCA ACAAGGACCT CAAGAAGTGC CTGACCACTC ACGCCCCCTG CTGGGGCACA 1080
GGAGGTGCCC CGGCTCCCAG AGAACCTAC TGTGTCATGT GA 1122

(23) INFORMATION FOR SEQ ID NO:22:

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 373 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

5 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Met | Ala | Asn | Thr | Thr | Gly | Glu | Pro | Glu | Glu | Val | Ser | Gly | Ala | Leu | Ser | |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| 10 | Pro | Pro | Ser | Ala | Ser | Ala | Tyr | Val | Lys | Leu | Val | Leu | Leu | Gly | Leu | Ile | |
| | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | Met | Cys | Val | Ser | Leu | Ala | Gly | Asn | Ala | Ile | Leu | Ser | Leu | Leu | Val | Leu | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| 15 | Lys | Glu | Arg | Ala | Leu | His | Lys | Ala | Pro | Tyr | Tyr | Phe | Leu | Leu | Asp | Leu | |
| | | 50 | | | | | 55 | | | | | 60 | | | | | |
| | Cys | Leu | Ala | Asp | Gly | Ile | Arg | Ser | Ala | Val | Cys | Phe | Pro | Phe | Val | Leu | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| | Ala | Ser | Val | Arg | His | Gly | Ser | Ser | Trp | Thr | Phe | Ser | Ala | Leu | Ser | Cys | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| 20 | Lys | Ile | Val | Ala | Phe | Met | Ala | Val | Leu | Phe | Cys | Phe | His | Ala | Ala | Phe | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| | Met | Leu | Phe | Cys | Ile | Ser | Val | Thr | Arg | Tyr | Met | Ala | Ile | Ala | His | His | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| 25 | Arg | Phe | Tyr | Ala | Lys | Arg | Met | Thr | Leu | Trp | Thr | Cys | Ala | Ala | Val | Ile | |
| | | 130 | | | | | 135 | | | | | 140 | | | | | |
| | Cys | Met | Ala | Trp | Thr | Leu | Ser | Val | Ala | Met | Ala | Phe | Pro | Pro | Val | Phe | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Asp | Val | Gly | Thr | Tyr | Lys | Phe | Ile | Arg | Glu | Glu | Asp | Gln | Cys | Ile | Phe | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| 30 | Glu | His | Arg | Tyr | Phe | Lys | Ala | Asn | Asp | Thr | Leu | Gly | Phe | Met | Leu | Met | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| | Leu | Ala | Val | Leu | Met | Ala | Ala | Thr | His | Ala | Val | Tyr | Gly | Lys | Leu | Leu | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| 35 | Leu | Phe | Glu | Tyr | Arg | His | Arg | Lys | Met | Lys | Pro | Val | Gln | Met | Val | Pro | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | Ala | Ile | Ser | Gln | Asn | Trp | Thr | Phe | His | Gly | Pro | Gly | Ala | Thr | Gly | Gln | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |

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[illegible]

(24) INFORMATION FOR SEQ ID NO:23:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1053 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

| | | | | | | | |
|----|-------------|------------|------------|-------------|-------------|------------|-----|
| | ATGGGCTTTGG | AACAGAACCA | GTCAACAGAT | TATTATTATG | AGGAAAATGA | AATGAATGGC | 60 |
| | ACTTATGACT | ACAGTCAATA | TGAATTGATC | TGTATCAAAG | AAGATGTCAG | AGAATTTGCA | 120 |
| | AAAGTTTTCC | TCCCTGTATT | CCTCACAATA | GCTTTCGTCA | TTGGACTTGC | AGGCAATTCC | 180 |
| 30 | ATGGTAGTGG | CAATTTATGC | CTATTACAAG | AAACAGAGAA | CCAAAACAGA | TGTGTACATC | 240 |
| | CTGAATTTGG | CTGTAGCAGA | TTTACTCCTT | CTATTCACCTC | TGCCTTTTTG | GGCTGTTAAT | 300 |
| | GCAGTTCATG | GGTGGGTTTT | AGGGAAAATA | ATGTGCAAAA | TAAC TTCAGC | CTTGTACACA | 360 |
| | CTAAACTTTG | TCTCTGGAAT | GCAGTTTCTG | GCTTGCATCA | GCATAGACAG | ATATGTGGCA | 420 |
| | GTAAC TAATG | TCCCCAGCCA | ATCAGGAGTG | GGAAAACCAT | GCTGGATCAT | CTGTTTCTGT | 480 |

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GTCTGGATGG CTGCCATCTT GCTGAGCATA CCCCAGCTGG TTTTTTATAC AGTAAATGAC 540
 AATGCTAGGT GCATTCCCAT TTTCCCCCGC TACCTAGGAA CATCAATGAA AGCATTGATT 600
 CAAATGCTAG AGATCTGCAT TGGATTTGTA GTACCCTTTC TTATTATGGG GGTGTGCTAC 660
 TTTATCACGG CAAGGACACT CATGAAGATG CCAAACATTA AAATATCTCG ACCCCTAAAA 720
 5 GTTCTGCTCA CAGTCGTTAT AGTTTTTATT GTCACTCAAC TGCCTTATAA CATTGTCAAG 780
 TTCTGCCGAG CCATAGACAT CATCTACTCC CTGATCACCA GCTGCAACAT GAGCAAACGC 840
 ATGGACATCG CCATCCAAGT CACAGAAAGC ATTGCACTCT TTCACAGCTG CCTCAACCCA 900
 ATCCTTTATG TTTTATGGG AGCATCTTTC AAAAAGTACG TTATGAAAGT GGCCAAGAAA 960
 TATGGGTCCT GGAGAAGACA GAGACAAAGT GTGGAGGAGT TTCCTTTTGA TTCTGAGGGT 1020
 10 CCTACAGAGC CAACCAGTAC TTTTAGCATT TAA 1053

(25) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 350 amino acids

(B) TYPE: amino acid

15 (C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

20 Met Ala Leu Glu Gln Asn Gln Ser Thr Asp Tyr Tyr Tyr Glu Glu Asn
 1 5 10 15
 Glu Met Asn Gly Thr Tyr Asp Tyr Ser Gln Tyr Glu Leu Ile Cys Ile
 20 25 30
 Lys Glu Asp Val Arg Glu Phe Ala Lys Val Phe Leu Pro Val Phe Leu
 35 40 45
 25 Thr Ile Ala Phe Val Ile Gly Leu Ala Gly Asn Ser Met Val Val Ala
 50 55 60
 Ile Tyr Ala Tyr Tyr Lys Lys Gln Arg Thr Lys Thr Asp Val Tyr Ile
 65 70 75 80
 30 Leu Asn Leu Ala Val Ala Asp Leu Leu Leu Leu Phe Thr Leu Pro Phe
 85 90 95
 Trp Ala Val Asn Ala Val His Gly Trp Val Leu Gly Lys Ile Met Cys
 100 105 110
 Lys Ile Thr Ser Ala Leu Tyr Thr Leu Asn Phe Val Ser Gly Met Gln

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| | 115 | 120 | 125 |
|----|---|-----|-------------|
| | Phe Leu Ala Cys Ile Ser Ile Asp Arg Tyr Val Ala Val Thr Asn Val | | |
| | 130 | 135 | 140 |
| 5 | Pro Ser Gln Ser Gly Val Gly Lys Pro Cys Trp Ile Ile Cys Phe Cys | | |
| | 145 | 150 | 155 160 |
| | Val Trp Met Ala Ala Ile Leu Leu Ser Ile Pro Gln Leu Val Phe Tyr | | |
| | | 165 | 170 175 |
| | Thr Val Asn Asp Asn Ala Arg Cys Ile Pro Ile Phe Pro Arg Tyr Leu | | |
| | | 180 | 185 190 |
| 10 | Gly Thr Ser Met Lys Ala Leu Ile Gln Met Leu Glu Ile Cys Ile Gly | | |
| | | 195 | 200 205 |
| | Phe Val Val Pro Phe Leu Ile Met Gly Val Cys Tyr Phe Ile Thr Ala | | |
| | | 210 | 215 220 |
| 15 | Arg Thr Leu Met Lys Met Pro Asn Ile Lys Ile Ser Arg Pro Leu Lys | | |
| | | 225 | 230 235 240 |
| | Val Leu Leu Thr Val Val Ile Val Phe Ile Val Thr Gln Leu Pro Tyr | | |
| | | 245 | 250 255 |
| | Asn Ile Val Lys Phe Cys Arg Ala Ile Asp Ile Ile Tyr Ser Leu Ile | | |
| | | 260 | 265 270 |
| 20 | Thr Ser Cys Asn Met Ser Lys Arg Met Asp Ile Ala Ile Gln Val Thr | | |
| | | 275 | 280 285 |
| | Glu Ser Ile Ala Leu Phe His Ser Cys Leu Asn Pro Ile Leu Tyr Val | | |
| | | 290 | 295 300 |
| 25 | Phe Met Gly Ala Ser Phe Lys Asn Tyr Val Met Lys Val Ala Lys Lys | | |
| | | 305 | 310 315 320 |
| | Tyr Gly Ser Trp Arg Arg Gln Arg Gln Ser Val Glu Glu Phe Pro Phe | | |
| | | 325 | 330 335 |
| | Asp Ser Glu Gly Pro Thr Glu Pro Thr Ser Thr Phe Ser Ile | | |
| | | 340 | 345 350 |

30 (26) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1116 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

ATGCCAGGAA ACGCCACCCC AGTGACCACC ACTGCCCCGT GGGCCTCCCT GGGCCTCTCC      60
GCCAAGACCT GCAACAACGT GTCCTTCGAA GAGAGCAGGA TAGTCCTGGT CGTGGTGTAC      120
AGCGCGGTGT GCACGCTGGG GGTGCCGGCC AACTGCCTGA CTGCGTGGCT GGCCTGCTG      180
5  CAGGTACTGC AGGGCAACGT GCTGGCCGTC TACCTGCTCT GCCTGGCACT CTGCGAACTG      240
CTGTACACAG GCACGCTGCC ACTCTGGGTC ATCTATATCC GCAACCAGCA CCGCTGGACC      300
CTAGGCCTGC TGGCCTCGAA GGTGACCGCC TACATCTTCT TCTGCAACAT CTACGTCAGC      360
ATCCTCTTCC TGTGCTGCAT CTCCTGCGAC CGCTTCGTGG CCGTGGTGTA CGCGCTGGAG      420
AGTCGGGGCC GCCGCCGCCG GAGGACCGCC ATCCTCATCT CCGCCTGCAT CTTCATCCTC      480
10  GTCGGGATCG TTCACTACCC GGTGTTCCAG ACGGAAGACA AGGAGACCTG CTTTGACATG      540
CTGCAGATGG ACAGCAGGAT TGCCGGGTAC TACTACGCCA GGTTCACCGT TGGCTTTGCC      600
ATCCCTCTCT CCATCATCGC CTTCAACAAC CACCGGATTT TCAGGAGCAT CAAGCAGAGC      660
ATGGGCTTAA GCGCTGCCCA GAAGGCCAAG GTGAAGCACT CGGCCATCGC GGTGGTTGTC      720
ATCTTCCTAG TCTGCTTCGC CCCGTACCAC CTGGTTCTCC TCGTCAAAGC CGCTGCCTTT      780
15  TCCTACTACA GAGGAGACAG GAACGCCATG TGCGGCTTGG AGGAAAGGCT GTACACAGCC      840
TCTGTGGTGT TTCTGTGCCT GTCCACGGTG AACGGCGTGG CTGACCCCAT TATCTACGTG      900
CTGGCCACGG ACCATTCCCG CCAAGAAGTG TCCAGAATCC ATAAGGGGTG GAAAGAGTGG      960
TCCATGAAGA CAGACGTCAC CAGGCTCACC CACAGCAGGG ACACCGAGGA GCTGCAGTCG     1020
CCCGTGGCCC TTGCAGACCA CTACACCTTC TCCAGGCCCG TGCACCCACC AGGGTCACCA     1080
20  TGCCCTGCAA AGAGGCTGAT TGAGGAGTCC TGCTGA                               1116

```

(28) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 371 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

30  Met Pro Gly Asn Ala Thr Pro Val Thr Thr Thr Ala Pro Trp Ala Ser
    1              5              10              15

```

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| | | |
|----|---|-------------|
| | Leu Gly Leu Ser Ala Lys Thr Cys Asn Asn Val Ser Phe Glu Glu Ser | |
| | 20 | 25 30 |
| | Arg Ile Val Leu Val Val Val Tyr Ser Ala Val Cys Thr Leu Gly Val | |
| | 35 | 40 45 |
| 5 | Pro Ala Asn Cys Leu Thr Ala Trp Leu Ala Leu Leu Gln Val Leu Gln | |
| | 50 | 55 60 |
| | Gly Asn Val Leu Ala Val Tyr Leu Leu Cys Leu Ala Leu Cys Glu Leu | |
| | 65 | 70 75 80 |
| 10 | Leu Tyr Thr Gly Thr Leu Pro Leu Trp Val Ile Tyr Ile Arg Asn Gln | |
| | 85 | 90 95 |
| | His Arg Trp Thr Leu Gly Leu Leu Ala Ser Lys Val Thr Ala Tyr Ile | |
| | 100 | 105 110 |
| | Phe Phe Cys Asn Ile Tyr Val Ser Ile Leu Phe Leu Cys Cys Ile Ser | |
| | 115 | 120 125 |
| 15 | Cys Asp Arg Phe Val Ala Val Val Tyr Ala Leu Glu Ser Arg Gly Arg | |
| | 130 | 135 140 |
| | Arg Arg Arg Arg Thr Ala Ile Leu Ile Ser Ala Cys Ile Phe Ile Leu | |
| | 145 | 150 155 160 |
| 20 | Val Gly Ile Val His Tyr Pro Val Phe Gln Thr Glu Asp Lys Glu Thr | |
| | 165 | 170 175 |
| | Cys Phe Asp Met Leu Gln Met Asp Ser Arg Ile Ala Gly Tyr Tyr Tyr | |
| | 180 | 185 190 |
| | Ala Arg Phe Thr Val Gly Phe Ala Ile Pro Leu Ser Ile Ile Ala Phe | |
| | 195 | 200 205 |
| 25 | Thr Asn His Arg Ile Phe Arg Ser Ile Lys Gln Ser Met Gly Leu Ser | |
| | 210 | 215 220 |
| | Ala Ala Gln Lys Ala Lys Val Lys His Ser Ala Ile Ala Val Val Val | |
| | 225 | 230 235 240 |
| 30 | Ile Phe Leu Val Cys Phe Ala Pro Tyr His Leu Val Leu Leu Val Lys | |
| | 245 | 250 255 |
| | Ala Ala Ala Phe Ser Tyr Tyr Arg Gly Asp Arg Asn Ala Met Cys Gly | |
| | 260 | 265 270 |
| | Leu Glu Glu Arg Leu Tyr Thr Ala Ser Val Val Phe Leu Cys Leu Ser | |
| | 275 | 280 285 |
| 35 | Thr Val Asn Gly Val Ala Asp Pro Ile Ile Tyr Val Leu Ala Thr Asp | |
| | 290 | 295 300 |

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His Ser Arg Gln Glu Val Ser Arg Ile His Lys Gly Trp Lys Glu Trp
 305 310 315 320
 Ser Met Lys Thr Asp Val Thr Arg Leu Thr His Ser Arg Asp Thr Glu
 325 330 335
 5 Glu Leu Gln Ser Pro Val Ala Leu Ala Asp His Tyr Thr Phe Ser Arg
 340 345 350
 Pro Val His Pro Pro Gly Ser Pro Cys Pro Ala Lys Arg Leu Ile Glu
 355 360 365
 10 Glu Ser Cys
 370

(28) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1113 base pairs
 (B) TYPE: nucleic acid
 15 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

ATGGCGAACT ATAGCCATGC AGCTGACAAC ATTTTGCAAA ATCTCTCGCC TCTAACAGCC 60
 20 TTTCTGAAAC TGACTTCCTT GGGTTTCATA ATAGGAGTCA GCGTGGTGGG CAACCTCCTG 120
 ATCTCCATTT TGCTAGTGAA AGATAAGACC TTGCATAGAG CACCTTACTA CTTCTGTGTT 180
 GATCTTTGCT GTTCAGATAT CCTCAGATCT GCAATTTGTT TCCCATTGTG GTTCAACTCT 240
 GTCAAAAATG GCTCTACCTG GACTTATGGG ACTCTGACTT GCAAAGTGAT TGCCTTTCTG 300
 GGGGTTTTGT CCTGTTTCCA CACTGCTTTC ATGCTCTTCT GCATCAGTGT CACCAGATAC 360
 25 TTAGCTATCG CCCATCACCG CTTCTATACA AAGAGGCTGA CCTTTTGGAC GTGTCTGGCT 420
 GTGATCTGTA TGGTGTGGAC TCTGTCTGTG GCCATGGCAT TTCCCCCGGT TTTAGACGTG 480
 GGCATTACT CATTATTAG GGAGGAAGAT CAATGCACCT TCCAACACCG CTCCTTCAGG 540
 GCTAATGATT CCTTAGGATT TATGCTGCTT CTTGCTCTCA TCCTCCTAGC CACACAGCTT 600
 GTCTACCTCA AGCTGATATT TTTCGTCCAC GATCGAAGAA AAATGAAGCC AGTCCAGTTT 660
 30 GTAGCAGCAG TCAGCCAGAA CTGGACTTTT CATGGTCCTG GAGCCAGTGG CCAGGCAGCT 720
 GCCAATTGGC TAGCAGGATT TGAAGGGGT CCCACACCAC CCACCTTGCT GGGCATCAGG 780
 CAAAATGCAA ACACCACAGG CAGAAGAAGG CTATTGGTCT TAGACGAGTT CAAAATGGAG 840

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AAAAGAATCA GCAGAATGTT CTATATAATG ACTTTTCTGT TTCTAACCTT GTGGGGCCCC 900
 TACCTGGTGG CCTGTTATTG GAGAGTTTTT GCAAGAGGGC CTGTAGTACC AGGGGGATTT 960
 CTAACAGCTG CTGTCTGGAT GAGTTTGTCC CAAGCAGGAA TCAATCCTTT TGTCTGCATT 1020
 TTCTCAAACA GGGAGCTGAG GCGCTGTTTC AGCACAACCC TTCTTTACTG CAGAAAATCC 1080
 5 AGGTTACCAA GGGAACCTTA CTGTGTTATA TGA 1113

(29) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 370 amino acids
 (B) TYPE: amino acid
 10 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

15 Met Ala Asn Tyr Ser His Ala Ala Asp Asn Ile Leu Gln Asn Leu Ser
 1 5 10 15
 Pro Leu Thr Ala Phe Leu Lys Leu Thr Ser Leu Gly Phe Ile Ile Gly
 20 25 30
 Val Ser Val Val Gly Asn Leu Leu Ile Ser Ile Leu Leu Val Lys Asp
 35 40 45
 20 Lys Thr Leu His Arg Ala Pro Tyr Tyr Phe Leu Leu Asp Leu Cys Cys
 50 55 60
 Ser Asp Ile Leu Arg Ser Ala Ile Cys Phe Pro Phe Val Phe Asn Ser
 65 70 75 80
 25 Val Lys Asn Gly Ser Thr Trp Thr Tyr Gly Thr Leu Thr Cys Lys Val
 85 90 95
 Ile Ala Phe Leu Gly Val Leu Ser Cys Phe His Thr Ala Phe Met Leu
 100 105 110
 Phe Cys Ile Ser Val Thr Arg Tyr Leu Ala Ile Ala His His Arg Phe
 115 120 125
 30 Tyr Thr Lys Arg Leu Thr Phe Trp Thr Cys Leu Ala Val Ile Cys Met
 130 135 140
 Val Trp Thr Leu Ser Val Ala Met Ala Phe Pro Pro Val Leu Asp Val
 145 150 155 160
 Gly Thr Tyr Ser Phe Ile Arg Glu Glu Asp Gln Cys Thr Phe Gln His

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| | 165 | 170 | 175 |
|----|---|-----|---------|
| | Arg Ser Phe Arg Ala Asn Asp Ser Leu Gly Phe Met Leu Leu Leu Ala | | |
| | 180 | 185 | 190 |
| 5 | Leu Ile Leu Leu Ala Thr Gln Leu Val Tyr Leu Lys Leu Ile Phe Phe | | |
| | 195 | 200 | 205 |
| | Val His Asp Arg Arg Lys Met Lys Pro Val Gln Phe Val Ala Ala Val | | |
| | 210 | 215 | 220 |
| | Ser Gln Asn Trp Thr Phe His Gly Pro Gly Ala Ser Gly Gln Ala Ala | | |
| | 225 | 230 | 235 240 |
| 10 | Ala Asn Trp Leu Ala Gly Phe Gly Arg Gly Pro Thr Pro Pro Thr Leu | | |
| | 245 | 250 | 255 |
| | Leu Gly Ile Arg Gln Asn Ala Asn Thr Thr Gly Arg Arg Arg Leu Leu | | |
| | 260 | 265 | 270 |
| 15 | Val Leu Asp Glu Phe Lys Met Glu Lys Arg Ile Ser Arg Met Phe Tyr | | |
| | 275 | 280 | 285 |
| | Ile Met Thr Phe Leu Phe Leu Thr Leu Trp Gly Pro Tyr Leu Val Ala | | |
| | 290 | 295 | 300 |
| | Cys Tyr Trp Arg Val Phe Ala Arg Gly Pro Val Val Pro Gly Gly Phe | | |
| | 305 | 310 | 315 320 |
| 20 | Leu Thr Ala Ala Val Trp Met Ser Phe Ala Gln Ala Gly Ile Asn Pro | | |
| | 325 | 330 | 335 |
| | Phe Val Cys Ile Phe Ser Asn Arg Glu Leu Arg Arg Cys Phe Ser Thr | | |
| | 340 | 345 | 350 |
| 25 | Thr Leu Leu Tyr Cys Arg Lys Ser Arg Leu Pro Arg Glu Pro Tyr Cys | | |
| | 355 | 360 | 365 |
| | Val Ile | | |
| | 370 | | |

(30) INFORMATION FOR SEQ ID NO:29:

- (i) SEQUENCE CHARACTERISTICS:
- 30 (A) LENGTH: 1080 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ATGCAGGTCC CGAACAGCAC CGGCCCGGAC AACGCGACGC TGCAGATGCT GCGGAACCCG 60

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GCGATCGCGG TGGCCCTGCC CGTGGTGTAC TCGCTGGTGG CGGCGGTCAG CATCCCAGGC 120
 AACCTCTTCT CTCTGTGGGT GCTGTGCCGG CGCATGGGGC CCAGATCCCC GTCGGTCATC 180
 TTCATGATCA ACCTGAGCGT CACGGACCTG ATGCTGGCCA GCGTGTGACC TTTCCAAATC 240
 TACTACCATT GCAACCGCCA CCACTGGGTA TTCGGGGTGC TGCTTTGCAA CGTGGTGACC 300
 5 GTGGCCTTTT ACGCAAACAT GTATTCCAGC ATCCTCACCA TGACCTGTAT CAGCGTGGAG 360
 CGCTTCCTGG GGGTCCTGTA CCCGCTCAGC TCCAAGCGCT GGCGCCGCCG TCGTTACGCG 420
 GTGGCCGCGT GTGCAGGGAC CTGGCTGCTG CTCCTGACCG CCCTGTGCCC GCTGGCGCGC 480
 ACCGATCTCA CCTACCCGGT GCACGCCCTG GGCATCATCA CCTGCTTCGA CGTCCTCAAG 540
 TGGACGATGC TCCCCAGCGT GGCCATGTGG GCCGTGTTCC TCTTCACCAT CTTTCATCTG 600
 10 CTGTTCTTCA TCCCGTTTCGT GATCACCGTG GCTTGTTACA CGGCCACCAT CCTCAAGCTG 660
 TTGCGCACGG AGGAGGCGCA CGGCCGGGAG CAGCGGAGGC GCGCGGTGGG CCTGGCCGCG 720
 GTGGTCTTGC TGGCCTTTGT CACCTGCTTC GCCCCAACA ACTTCGTGCT CCTGGCGCAC 780
 ATCGTGAGCC GCCTGTTCTA CGGCAAGAGC TACTACCACG TGTACAAGCT CACGCTGTGT 840
 CTCAGCTGCC TCAACAACTG TCTGGACCCG TTTGTTTATT ACTTTGCGTC CCGGGAATTC 900
 15 CAGCTGCGCC TGCGGGAATA TTTGGGCTGC CGCCGGGTGC CCAGAGACAC CCTGGACACG 960
 CGCCGCGAGA GCCTCTTCTC CGCCAGGACC ACGTCCGTGC GCTCCGAGGC CGGTGCGCAC 1020
 CCTGAAGGGA TGGAGGGAGC CACCAGGCCC GGCTCCAGA GGCAGGAGAG TGTGTTCTGA 1080

(31) INFORMATION FOR SEQ ID NO:30:

- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 359 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Met Gln Val Pro Asn Ser Thr Gly Pro Asp Asn Ala Thr Leu Gln Met
 1 5 10 15
 Leu Arg Asn Pro Ala Ile Ala Val Ala Leu Pro Val Val Tyr Ser Leu
 20 25 30
 30 Val Ala Ala Val Ser Ile Pro Gly Asn Leu Phe Ser Leu Trp Val Leu

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| | 35 | 40 | 45 |
|----|---|-----|-------------|
| | Cys Arg Arg Met Gly Pro Arg Ser Pro Ser Val Ile Phe Met Ile Asn | | |
| | 50 | 55 | 60 |
| 5 | Leu Ser Val Thr Asp Leu Met Leu Ala Ser Val Leu Pro Phe Gln Ile | | |
| | 65 | 70 | 75 80 |
| | Tyr Tyr His Cys Asn Arg His His Trp Val Phe Gly Val Leu Leu Cys | | |
| | | 85 | 90 95 |
| | Asn Val Val Thr Val Ala Phe Tyr Ala Asn Met Tyr Ser Ser Ile Leu | | |
| | | 100 | 105 110 |
| 10 | Thr Met Thr Cys Ile Ser Val Glu Arg Phe Leu Gly Val Leu Tyr Pro | | |
| | | 115 | 120 125 |
| | Leu Ser Ser Lys Arg Trp Arg Arg Arg Arg Tyr Ala Val Ala Ala Cys | | |
| | | 130 | 135 140 |
| 15 | Ala Gly Thr Trp Leu Leu Leu Leu Thr Ala Leu Cys Pro Leu Ala Arg | | |
| | | 145 | 150 155 160 |
| | Thr Asp Leu Thr Tyr Pro Val His Ala Leu Gly Ile Ile Thr Cys Phe | | |
| | | 165 | 170 175 |
| | Asp Val Leu Lys Trp Thr Met Leu Pro Ser Val Ala Met Trp Ala Val | | |
| | | 180 | 185 190 |
| 20 | Phe Leu Phe Thr Ile Phe Ile Leu Leu Phe Leu Ile Pro Phe Val Ile | | |
| | | 195 | 200 205 |
| | Thr Val Ala Cys Tyr Thr Ala Thr Ile Leu Lys Leu Leu Arg Thr Glu | | |
| | | 210 | 215 220 |
| 25 | Glu Ala His Gly Arg Glu Gln Arg Arg Arg Ala Val Gly Leu Ala Ala | | |
| | | 225 | 230 235 240 |
| | Val Val Leu Leu Ala Phe Val Thr Cys Phe Ala Pro Asn Asn Phe Val | | |
| | | 245 | 250 255 |
| | Leu Leu Ala His Ile Val Ser Arg Leu Phe Tyr Gly Lys Ser Tyr Tyr | | |
| | | 260 | 265 270 |
| 30 | His Val Tyr Lys Leu Thr Leu Cys Leu Ser Cys Leu Asn Asn Cys Leu | | |
| | | 275 | 280 285 |
| | Asp Pro Phe Val Tyr Tyr Phe Ala Ser Arg Glu Phe Gln Leu Arg Leu | | |
| | | 290 | 295 300 |
| 35 | Arg Glu Tyr Leu Gly Cys Arg Arg Val Pro Arg Asp Thr Leu Asp Thr | | |
| | | 305 | 310 315 320 |
| | Arg Arg Glu Ser Leu Phe Ser Ala Arg Thr Thr Ser Val Arg Ser Glu | | |
| | | 325 | 330 335 |

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Ala Gly Ala His Pro Glu Gly Met Glu Gly Ala Thr Arg Pro Gly Leu
 340 345 350

Gln Arg Gln Glu Ser Val Phe
 355

5 (32) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1503 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ATGGAGCGTC CCTGGGAGGA CAGCCCAGGC CCGGAGGGGG CAGCTGAGGG CTCGCCTGTG 60
 CCAGTCGCCG CCGGGGCGCG CTCCGGTGCC GCGGCGAGTG GCACAGGCTG GCAGCCATGG 120
 15 GCTGAGTGCC CGGGACCCAA GGGGAGGGGG CAACTGCTGG CGACCGCCGG CCCTTTGCGT 180
 CGCTGGCCCCG CCCCCTCGCC TGCCAGCTCC AGCCCCGCCC CCGGAGCGGC GTCCGCTCAC 240
 TCGGTTCAAG GCAGCGCGAC TGCGGGTGCC GCACGACCAG GGCGCAGACC TTGGGGCGCG 300
 CGGCCCCATGG AGTCGGGGCT GCTGCGGCCG GCGCCGGTGA GCGAGGTCAT CGTCCTGCAT 360
 TACAACTACA CCGGCAAGCT CCGCGGTGCG AGCTACCAGC CGGGTGCCGG CCTGCGCGCC 420
 20 GACGCCGTGG TGTGCCTGGC GGTGTGCGCC TTCATCGTGC TAGAGAATCT AGCCGTGTTG 480
 TTGGTGCTCG GACGCCACCC GCGCTTCCAC GCTCCCATGT TCCTGCTCCT GGGCAGCCTC 540
 ACGTTGTCCG ATCTGCTGGC AGGCGCCGCC TACGCCGCCA ACATCCTACT GTCGGGGCCG 600
 CTCACGCTGA AACTGTCCCC CGCGCTCTGG TTCGCACGGG AGGGAGGCGT CTTGCTGGCA 660
 CTCCTGCGT CCGTGCTGAG CCTCCTGGCC ATCGCGCTGG AGCGCAGCCT CACCATGGCG 720
 25 CGCAGGGGGC CCGCGCCCGT CTCCAGTCGG GGGCGCACGC TGGCGATGGC AGCCGCGGCC 780
 TGGGGCGTGT CGCTGCTCCT CGGGCTCCTG CCAGCGCTGG GCTGGAATTG CCTGGGTCGC 840
 CTGGACGCTT GCTCCACTGT CTTGCCGCTC TACGCCAAGG CCTACGTGCT CTTCTGCGTG 900
 CTCGCCTTCG TGGGCATCCT GGCCGCGATC TGTGCACTCT ACGCGCGCAT CTA CTGCCAG 960
 GTACGCGCCA ACGCGCGGCG CCTGCCGGCA CGGCCCGGGA CTGCGGGGAC CACCTCGACC 1020
 30 CGGGCGCGTC GCAAGCCGCG CTCTCTGGCC TTGCTGCGCA CGCTCAGCGT GGTGCTCCTG 1080

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GCCTTTGTGG CATGTTGGGG CCCCCTCTTC CTGCTGCTGT TGCTCGACGT GGC GTGCCCCG 1140
GCGCGCACCT GTCCTGTACT CCTGCAGGCC GATCCCTTCC TGGGACTGGC CATGGCCAAC 1200
TCACTTCTGA ACCCCATCAT CTACACGCTC ACCAACCGCG ACCTGCGCCA CGCGCTCCTG 1260
CGCCTGGTCT GCTGCGGACG CCACTCCTGC GGCAGAGACC CGAGTGGCTC CCAGCAGTCG 1320
5 GCGAGCGCGG CTGAGGCTTC CGGGGGCCTG CGCCGCTGCC TGCCCCCGGG CCTTGATGGG 1380
AGCTTCAGCG GCTCGGAGCG CTCATCGCCC CAGCGCGACG GGCTGGACAC CAGCGGCTCC 1440
ACAGGCAGCC CCGGTGCACC CACAGCCGCC CGGACTCTGG TATCAGAACC GGCTGCAGAC 1500
TGA 1503

```

(33) INFORMATION FOR SEQ ID NO:32:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 500 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

```

Met Glu Arg Pro Trp Glu Asp Ser Pro Gly Pro Glu Gly Ala Ala Glu
1           5           10           15

Gly Ser Pro Val Pro Val Ala Ala Gly Ala Arg Ser Gly Ala Ala Ala
20           20           25           30

Ser Gly Thr Gly Trp Gln Pro Trp Ala Glu Cys Pro Gly Pro Lys Gly
35           40           45

Arg Gly Gln Leu Leu Ala Thr Ala Gly Pro Leu Arg Arg Trp Pro Ala
50           55           60

25 Pro Ser Pro Ala Ser Ser Ser Pro Ala Pro Gly Ala Ala Ser Ala His
65           70           75           80

Ser Val Gln Gly Ser Ala Thr Ala Gly Gly Ala Arg Pro Gly Arg Arg
85           90           95

30 Pro Trp Gly Ala Arg Pro Met Glu Ser Gly Leu Leu Arg Pro Ala Pro
100          105          110

Val Ser Glu Val Ile Val Leu His Tyr Asn Tyr Thr Gly Lys Leu Arg
115          120          125

Gly Ala Ser Tyr Gln Pro Gly Ala Gly Leu Arg Ala Asp Ala Val Val
130          135          140

```

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| | | | | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | Cys | Leu | Ala | Val | Cys | Ala | Phe | Ile | Val | Leu | Glu | Asn | Leu | Ala | Val | Leu | 145 | 150 | 155 | 160 |
| | Leu | Val | Leu | Gly | Arg | His | Pro | Arg | Phe | His | Ala | Pro | Met | Phe | Leu | Leu | 165 | 170 | 175 | |
| 5 | Leu | Gly | Ser | Leu | Thr | Leu | Ser | Asp | Leu | Leu | Ala | Gly | Ala | Ala | Tyr | Ala | 180 | 185 | 190 | |
| | Ala | Asn | Ile | Leu | Leu | Ser | Gly | Pro | Leu | Thr | Leu | Lys | Leu | Ser | Pro | Ala | 195 | 200 | 205 | |
| 10 | Leu | Trp | Phe | Ala | Arg | Glu | Gly | Gly | Val | Phe | Val | Ala | Leu | Thr | Ala | Ser | 210 | 215 | 220 | |
| | Val | Leu | Ser | Leu | Leu | Ala | Ile | Ala | Leu | Glu | Arg | Ser | Leu | Thr | Met | Ala | 225 | 230 | 235 | 240 |
| | Arg | Arg | Gly | Pro | Ala | Pro | Val | Ser | Ser | Arg | Gly | Arg | Thr | Leu | Ala | Met | 245 | 250 | 255 | |
| 15 | Ala | Ala | Ala | Ala | Trp | Gly | Val | Ser | Leu | Leu | Leu | Gly | Leu | Leu | Pro | Ala | 260 | 265 | 270 | |
| | Leu | Gly | Trp | Asn | Cys | Leu | Gly | Arg | Leu | Asp | Ala | Cys | Ser | Thr | Val | Leu | 275 | 280 | 285 | |
| 20 | Pro | Leu | Tyr | Ala | Lys | Ala | Tyr | Val | Leu | Phe | Cys | Val | Leu | Ala | Phe | Val | 290 | 295 | 300 | |
| | Gly | Ile | Leu | Ala | Ala | Ile | Cys | Ala | Leu | Tyr | Ala | Arg | Ile | Tyr | Cys | Gln | 305 | 310 | 315 | 320 |
| | Val | Arg | Ala | Asn | Ala | Arg | Arg | Leu | Pro | Ala | Arg | Pro | Gly | Thr | Ala | Gly | 325 | 330 | 335 | |
| 25 | Thr | Thr | Ser | Thr | Arg | Ala | Arg | Arg | Lys | Pro | Arg | Ser | Leu | Ala | Leu | Leu | 340 | 345 | 350 | |
| | Arg | Thr | Leu | Ser | Val | Val | Leu | Leu | Ala | Phe | Val | Ala | Cys | Trp | Gly | Pro | 355 | 360 | 365 | |
| 30 | Leu | Phe | Leu | Leu | Leu | Leu | Leu | Asp | Val | Ala | Cys | Pro | Ala | Arg | Thr | Cys | 370 | 375 | 380 | |
| | Pro | Val | Leu | Leu | Gln | Ala | Asp | Pro | Phe | Leu | Gly | Leu | Ala | Met | Ala | Asn | 385 | 390 | 395 | 400 |
| | Ser | Leu | Leu | Asn | Pro | Ile | Ile | Tyr | Thr | Leu | Thr | Asn | Arg | Asp | Leu | Arg | 405 | 410 | 415 | |
| 35 | His | Ala | Leu | Leu | Arg | Leu | Val | Cys | Cys | Gly | Arg | His | Ser | Cys | Gly | Arg | 420 | 425 | 430 | |
| | Asp | Pro | Ser | Gly | Ser | Gln | Gln | Ser | Ala | Ser | Ala | Ala | Glu | Ala | Ser | Gly | | | | |

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435 440 445
 Gly Leu Arg Arg Cys Leu Pro Pro Gly Leu Asp Gly Ser Phe Ser Gly
 450 455 460
 Ser Glu Arg Ser Ser Pro Gln Arg Asp Gly Leu Asp Thr Ser Gly Ser
 5 465 470 475 480
 Thr Gly Ser Pro Gly Ala Pro Thr Ala Ala Arg Thr Leu Val Ser Glu
 485 490 495
 Pro Ala Ala Asp
 500

10 (34) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1029 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

ATGCAAGCCG TCGACAATCT CACCTCTGCG CCTGGGAACA CCAGTCTGTG CACCAGAGAC 60
 TACAAAATCA CCCAGGTCCT CTTCCCACTG CTCTACACTG TCCTGTTTTT TGTTGGACTT 120
 20 ATCACAAATG GCCTGGCGAT GAGGATTTTC TTTCAAATCC GGAGTAAATC AAACCTTTATT 180
 ATTTTTCTTA AGAACACAGT CATTTCTGAT CTTCTCATGA TTCTGACTTT TCCATTCAAA 240
 ATTCTTAGTG ATGCCAAACT GGGAACAGGA CCACTGAGAA CTTTTGTGTG TCAAGTTACC 300
 TCCGTCATAT TTTATTTTAC AATGTATATC AGTATTTTCT TCCTGGGACT GATAACTATC 360
 GATCGCTACC AGAAGACCAC CAGGCCATTT AAAACATCCA ACCCCAAAAA TCTCTTGGGG 420
 25 GCTAAGATTC TCTCTGTTGT CATCTGGGCA TTCATGTTCT TACTCTCTTT GCCTAACATG 480
 ATTCTGACCA ACAGGCAGCC GAGAGACAAG AATGTGAAGA AATGCTCTTT CCTTAAATCA 540
 GAGTTCGGTC TAGTCTGGCA TGAAATAGTA AATTACATCT GTCAAGTCAT TTTCTGGATT 600
 AATTTCTTAA TTGTTATTGT ATGTTATACA CTCATTACAA AAGAACTGTA CCGGTCATAC 660
 GTAAGAACGA GGGGTGTAGG TAAAGTCCCC AGGAAAAAGG TGAACGTCAA AGTTTTCATT 720
 30 ATCATTGCTG TATTCTTTAT TTGTTTTGTT CCTTTCCATT TTGCCCCGAAT TCCTTACACC 780
 CTGAGCCAAA CCCGGGATGT CTTTGACTGC ACTGCTGAAA ATACTCTGTT CTATGTGAAA 840

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GAGAGCACTC TGTGGTTAAC TTCCTTAAAT GCATGCCTGG ATCCGTTCAT CTATTTTTTC 900
 CTTTGCAAGT CCTTCAGAAA TTCCTTGATA AGTATGCTGA AGTGCCCCAA TTCTGCAACA 960
 TCTCTGTCCC AGGACAATAG GAAAAAAGAA CAGGATGGTG GTGACCCAAA TGAAGAGACT 1020
 CCAATGTAA 1029

5 (35) INFORMATION FOR SEQ ID NO:34:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 342 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

10

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Met Gln Ala Val Asp Asn Leu Thr Ser Ala Pro Gly Asn Thr Ser Leu
 1 5 10 15
 15 Cys Thr Arg Asp Tyr Lys Ile Thr Gln Val Leu Phe Pro Leu Leu Tyr
 20 25 30
 Thr Val Leu Phe Phe Val Gly Leu Ile Thr Asn Gly Leu Ala Met Arg
 35 40 45
 20 Ile Phe Phe Gln Ile Arg Ser Lys Ser Asn Phe Ile Ile Phe Leu Lys
 50 55 60
 Asn Thr Val Ile Ser Asp Leu Leu Met Ile Leu Thr Phe Pro Phe Lys
 65 70 75 80
 Ile Leu Ser Asp Ala Lys Leu Gly Thr Gly Pro Leu Arg Thr Phe Val
 85 90 95
 25 Cys Gln Val Thr Ser Val Ile Phe Tyr Phe Thr Met Tyr Ile Ser Ile
 100 105 110
 Ser Phe Leu Gly Leu Ile Thr Ile Asp Arg Tyr Gln Lys Thr Thr Arg
 115 120 125
 30 Pro Phe Lys Thr Ser Asn Pro Lys Asn Leu Leu Gly Ala Lys Ile Leu
 130 135 140
 Ser Val Val Ile Trp Ala Phe Met Phe Leu Leu Ser Leu Pro Asn Met
 145 150 155 160
 Ile Leu Thr Asn Arg Gln Pro Arg Asp Lys Asn Val Lys Lys Cys Ser
 165 170 175
 35 Phe Leu Lys Ser Glu Phe Gly Leu Val Trp His Glu Ile Val Asn Tyr

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| | 180 | 185 | 190 |
|----|---|-------------------------|-------------|
| | Ile Cys Gln Val Ile Phe Trp | Ile Asn Phe Leu Ile Val | Ile Val Cys |
| | 195 | 200 | 205 |
| 5 | Tyr Thr Leu Ile Thr Lys Glu Leu Tyr Arg Ser Tyr Val Arg Thr Arg | | |
| | 210 | 215 | 220 |
| | Gly Val Gly Lys Val Pro Arg Lys Lys Val Asn Val Lys Val Phe Ile | | |
| | 225 | 230 | 235 240 |
| | Ile Ile Ala Val Phe Phe Ile Cys Phe Val Pro Phe His Phe Ala Arg | | |
| | 245 | 250 | 255 |
| 10 | Ile Pro Tyr Thr Leu Ser Gln Thr Arg Asp Val Phe Asp Cys Thr Ala | | |
| | 260 | 265 | 270 |
| | Glu Asn Thr Leu Phe Tyr Val Lys Glu Ser Thr Leu Trp Leu Thr Ser | | |
| | 275 | 280 | 285 |
| 15 | Leu Asn Ala Cys Leu Asp Pro Phe Ile Tyr Phe Phe Leu Cys Lys Ser | | |
| | 290 | 295 | 300 |
| | Phe Arg Asn Ser Leu Ile Ser Met Leu Lys Cys Pro Asn Ser Ala Thr | | |
| | 305 | 310 | 315 320 |
| | Ser Leu Ser Gln Asp Asn Arg Lys Lys Glu Gln Asp Gly Gly Asp Pro | | |
| | 325 | 330 | 335 |
| 20 | Asn Glu Glu Thr Pro Met | | |
| | 340 | | |

(36) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1077 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

| | | |
|----|---|-----|
| 30 | ATGTCGGTCT GCTACCGTCC CCCAGGGAAC GAGACACTGC TGAGCTGGAA GACTTCGCGG | 60 |
| | GCCACAGGCA CAGCCTTCCT GCTGCTGGCG GCGCTGCTGG GGCTGCCTGG CAACGGCTTC | 120 |
| | GTGGTGTGGA GCTTGGCGGG CTGGCGGCCT GCACGGGGGC GACCGCTGGC GGCCACGCTT | 180 |
| | GTGCTGCACC TGGCGCTGGC CGACGGCGCG GTGCTGCTGC TCACGCCGCT CTTTGTGGCC | 240 |
| | TTCCTGACCC GGCAGGCCTG GCCGCTGGGC CAGGCGGGCT GCAAGGCGGT GTACTACGTG | 300 |

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TGC GCGCTCA GCATGTACGC CAGCGTGCTG CTCACCGGCC TGCTCAGCCT GCAGCGCTGC 360
 CTCGCAGTCA CCCGCCCTT CCTGGCGCCT CGGCTGCGCA GCGCGGCCCT GGCCCGCCGC 420
 CTGCTGCTGG CGGTCTGGCT GGCCGCCCTG TTGCTCGCCG TCCCGGCCGC CGTCTACCGC 480
 CACCTGTGGA GGGACCGCGT ATGCCAGCTG TGCCACCCGT CGCCGGTCCA CGCCGCCGCC 540
 5 CACCTGAGCC TGGAGACTCT GACCGCTTTC GTGCTTCCTT TCGGGCTGAT GCTCGGCTGC 600
 TACAGCGTGA CGCTGGCACG GCTGCGGGG GCGCGCTGGG GCTCCGGGCG GCACGGGGCG 660
 CGGGTGGGCC GGCTGGTGAG CGCCATCGTG CTTGCCTTCG GCTTGCTCTG GGCCCCCTAC 720
 CACGCAGTCA ACCTTCTGCA GGCGGTCGCA GCGCTGGCTC CACCGGAAGG GGCCTTGGCG 780
 AAGCTGGGCG GAGCCGGCCA GGCGGCGCGA GCGGGAATA CGGCCTTGGC CTTCTTCAGT 840
 10 TCTAGCGTCA ACCCGGTGCT CTACGTCTTC ACCGCTGGAG ATCTGCTGCC CCGGGCAGGT 900
 CCCCGTTTCC TCACGCGGCT CTTGAAGGC TCTGGGGAGG CCCGAGGGGG CGGCCGCTCT 960
 AGGGAAGGGA CCATGGAGCT CCGAACTACC CCTCAGCTGA AAGTGGTGGG GCAGGGCCGC 1020
 GGCAATGGAG ACCCGGGGGG TGGGATGGAG AAGGACGGTC CGGAATGGGA CCTTTGA 1077

(37) INFORMATION FOR SEQ ID NO:36:

- 15 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 358 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Met Ser Val Cys Tyr Arg Pro Pro Gly Asn Glu Thr Leu Leu Ser Trp
 1 5 10 15
 Lys Thr Ser Arg Ala Thr Gly Thr Ala Phe Leu Leu Leu Ala Ala Leu
 25 20 25 30
 Leu Gly Leu Pro Gly Asn Gly Phe Val Val Trp Ser Leu Ala Gly Trp
 35 40 45
 Arg Pro Ala Arg Gly Arg Pro Leu Ala Ala Thr Leu Val Leu His Leu
 50 55 60
 30 Ala Leu Ala Asp Gly Ala Val Leu Leu Leu Thr Pro Leu Phe Val Ala
 65 70 75 80
 Phe Leu Thr Arg Gln Ala Trp Pro Leu Gly Gln Ala Gly Cys Lys Ala

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| | 85 | 90 | 95 |
|----|---|-----|-----|
| | Val Tyr Tyr Val Cys Ala Leu Ser Met Tyr Ala Ser Val Leu Leu Thr | | |
| | 100 | 105 | 110 |
| 5 | Gly Leu Leu Ser Leu Gln Arg Cys Leu Ala Val Thr Arg Pro Phe Leu | | |
| | 115 | 120 | 125 |
| | Ala Pro Arg Leu Arg Ser Pro Ala Leu Ala Arg Arg Leu Leu Leu Ala | | |
| | 130 | 135 | 140 |
| | Val Trp Leu Ala Ala Leu Leu Leu Ala Val Pro Ala Ala Val Tyr Arg | | |
| | 145 | 150 | 155 |
| 10 | His Leu Trp Arg Asp Arg Val Cys Gln Leu Cys His Pro Ser Pro Val | | |
| | 165 | 170 | 175 |
| | His Ala Ala Ala His Leu Ser Leu Glu Thr Leu Thr Ala Phe Val Leu | | |
| | 180 | 185 | 190 |
| 15 | Pro Phe Gly Leu Met Leu Gly Cys Tyr Ser Val Thr Leu Ala Arg Leu | | |
| | 195 | 200 | 205 |
| | Arg Gly Ala Arg Trp Gly Ser Gly Arg His Gly Ala Arg Val Gly Arg | | |
| | 210 | 215 | 220 |
| | Leu Val Ser Ala Ile Val Leu Ala Phe Gly Leu Leu Trp Ala Pro Tyr | | |
| | 225 | 230 | 235 |
| 20 | His Ala Val Asn Leu Leu Gln Ala Val Ala Ala Leu Ala Pro Pro Glu | | |
| | 245 | 250 | 255 |
| | Gly Ala Leu Ala Lys Leu Gly Gly Ala Gly Gln Ala Ala Arg Ala Gly | | |
| | 260 | 265 | 270 |
| 25 | Thr Thr Ala Leu Ala Phe Phe Ser Ser Ser Val Asn Pro Val Leu Tyr | | |
| | 275 | 280 | 285 |
| | Val Phe Thr Ala Gly Asp Leu Leu Pro Arg Ala Gly Pro Arg Phe Leu | | |
| | 290 | 295 | 300 |
| | Thr Arg Leu Phe Glu Gly Ser Gly Glu Ala Arg Gly Gly Gly Arg Ser | | |
| | 305 | 310 | 315 |
| 30 | Arg Glu Gly Thr Met Glu Leu Arg Thr Thr Pro Gln Leu Lys Val Val | | |
| | 325 | 330 | 335 |
| | Gly Gln Gly Arg Gly Asn Gly Asp Pro Gly Gly Gly Met Glu Lys Asp | | |
| | 340 | 345 | 350 |
| 35 | Gly Pro Glu Trp Asp Leu | | |
| | 355 | | |

(38) INFORMATION FOR SEQ ID NO:37:

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1005 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

| | | |
|----|--|------|
| | ATGCTGGGGA TCATGGCATG GAATGCAACT TGCAAAAACT GGCTGGCAGC AGAGGCTGCC | 60 |
| | CTGGAAAAGT ACTACCTTTC CATTTTTTAT GGGATTGAGT TCGTTGTGGG AGTCCTTGGA | 120 |
| 10 | AATACCATTG TTGTTTACGG CTACATCTTC TCTCTGAAGA ACTGGAACAG CAGTAATATT | 180 |
| | TATCTCTTTA ACCTCTCTGT CTCTGACTTA GCTTTTCTGT GCACCCTCCC CATGCTGATA | 240 |
| | AGGAGTTATG CCAATGGAAA CTGGATATAT GGAGACGTGC TCTGCATAAG CAACCGATAT | 300 |
| | GTGCTTCATG CCAACCTCTA TACCAGCATT CTCTTTCTCA CTTTATCAG CATAGATCGA | 360 |
| | TACTTGATAA TTAAGTATCC TTTCCGAGAA CACCTTCTGC AAAAGAAAGA GTTTGCTATT | 420 |
| 15 | TTAATCTCCT TGGCCATTTG GGTTTTAGTA ACCTTAGAGT TACTACCCAT ACTTCCCCTT | 480 |
| | ATAAATCCTG TTATAACTGA CAATGGCACC ACCTGTAATG ATTTTGCAAG TTCTGGAGAC | 540 |
| | CCCAACTACA ACCTCATTTA CAGCATGTGT CTAACACTGT TGGGGTTCCT TATTCCTCTT | 600 |
| | TTTGTGATGT GTTTCTTTTA TTACAAGATT GCTCTCTTCC TAAAGCAGAG GAATAGGCAG | 660 |
| | GTTGCTACTG CTCTGCCCCCT TGAAAAGCCT CTCAACTTGG TCATCATGGC AGTGGTAATC | 720 |
| 20 | TTCTCTGTGC TTTTACACC CTATCACGTC ATGCGGAATG TGAGGATCGC TTCACGCCTG | 780 |
| | GGGAGTTGGA AGCAGTATCA GTGCACTCAG GTCGTCATCA ACTCCTTTTA CATTGTGACA | 840 |
| | CGGCCTTTGG CCTTTCTGAA CAGTGTCATC AACCTGTCT TCTATTTTCT TTTGGGAGAT | 900 |
| | CACTTCAGGG ACATGCTGAT GAATCAACTG AGACACAACT TCAAATCCCT TACATCCTTT | 960 |
| | AGCAGATGGG CTCATGAACT CCTACTTTCA TTCAGAGAAA AGTGA | 1005 |

25 (39) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 334 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

30

(ii) MOLECULE TYPE: protein

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Met | Leu | Gly | Ile | Met | Ala | Trp | Asn | Ala | Thr | Cys | Lys | Asn | Trp | Leu | Ala | |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| 5 | Ala | Glu | Ala | Ala | Leu | Glu | Lys | Tyr | Tyr | Leu | Ser | Ile | Phe | Tyr | Gly | Ile | |
| | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | Glu | Phe | Val | Val | Gly | Val | Leu | Gly | Asn | Thr | Ile | Val | Val | Tyr | Gly | Tyr | |
| | | | 35 | | | | | 40 | | | | | 45 | | | | |
| | Ile | Phe | Ser | Leu | Lys | Asn | Trp | Asn | Ser | Ser | Asn | Ile | Tyr | Leu | Phe | Asn | |
| | | 50 | | | | | 55 | | | | | 60 | | | | | |
| 10 | Leu | Ser | Val | Ser | Asp | Leu | Ala | Phe | Leu | Cys | Thr | Leu | Pro | Met | Leu | Ile | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| | Arg | Ser | Tyr | Ala | Asn | Gly | Asn | Trp | Ile | Tyr | Gly | Asp | Val | Leu | Cys | Ile | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| 15 | Ser | Asn | Arg | Tyr | Val | Leu | His | Ala | Asn | Leu | Tyr | Thr | Ser | Ile | Leu | Phe | |
| | | | 100 | | | | | | 105 | | | | | 110 | | | |
| | Leu | Thr | Phe | Ile | Ser | Ile | Asp | Arg | Tyr | Leu | Ile | Ile | Lys | Tyr | Pro | Phe | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | Arg | Glu | His | Leu | Leu | Gln | Lys | Lys | Glu | Phe | Ala | Ile | Leu | Ile | Ser | Leu | |
| | | 130 | | | | | 135 | | | | | 140 | | | | | |
| 20 | Ala | Ile | Trp | Val | Leu | Val | Thr | Leu | Glu | Leu | Leu | Pro | Ile | Leu | Pro | Leu | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Ile | Asn | Pro | Val | Ile | Thr | Asp | Asn | Gly | Thr | Thr | Cys | Asn | Asp | Phe | Ala | |
| | | | | 165 | | | | | 170 | | | | | | 175 | | |
| 25 | Ser | Ser | Gly | Asp | Pro | Asn | Tyr | Asn | Leu | Ile | Tyr | Ser | Met | Cys | Leu | Thr | |
| | | | 180 | | | | | | 185 | | | | | 190 | | | |
| | Leu | Leu | Gly | Phe | Leu | Ile | Pro | Leu | Phe | Val | Met | Cys | Phe | Phe | Tyr | Tyr | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| | Lys | Ile | Ala | Leu | Phe | Leu | Lys | Gln | Arg | Asn | Arg | Gln | Val | Ala | Thr | Ala | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| 30 | Leu | Pro | Leu | Glu | Lys | Pro | Leu | Asn | Leu | Val | Ile | Met | Ala | Val | Val | Ile | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Phe | Ser | Val | Leu | Phe | Thr | Pro | Tyr | His | Val | Met | Arg | Asn | Val | Arg | Ile | |
| | | | | 245 | | | | | | 250 | | | | | 255 | | |
| 35 | Ala | Ser | Arg | Leu | Gly | Ser | Trp | Lys | Gln | Tyr | Gln | Cys | Thr | Gln | Val | Val | |
| | | | 260 | | | | | | 265 | | | | | 270 | | | |
| | Ile | Asn | Ser | Phe | Tyr | Ile | Val | Thr | Arg | Pro | Leu | Ala | Phe | Leu | Asn | Ser | |

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| | | | | | |
|---|---|-----|-----|-----|---------|
| | 275 | | 280 | | 285 |
| | Val Ile Asn Pro Val Phe Tyr Phe Leu Leu Gly Asp His Phe Arg Asp | | | | |
| | 290 | | 295 | | 300 |
| 5 | Met Leu Met Asn Gln Leu Arg His Asn Phe Lys Ser Leu Thr Ser Phe | | | | |
| | 305 | | 310 | | 315 320 |
| | Ser Arg Trp Ala His Glu Leu Leu Leu Ser Phe Arg Glu Lys | | | | |
| | | 325 | | 330 | |

(40) INFORMATION FOR SEQ ID NO:39:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 1296 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

| | | |
|----|--|-----|
| | ATGCAGGCGC TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG | 60 |
| | ACGCGGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG | 120 |
| | CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC | 180 |
| | TTTGGAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC | 240 |
| 20 | AACATCTTTA TCTGCTCCTT GGCCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC | 300 |
| | GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGGG GTGCTTTCAT TTGCAAGATG | 360 |
| | GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACTATGAC CTGCATTGCT | 420 |
| | GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTTAAAATGA AGTGGCAATA CACCAACCGA | 480 |
| | AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCATG | 540 |
| 25 | TGGCACGTGC AACAACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC | 600 |
| | TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC | 660 |
| | ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAAT TGGTTATGAA | 720 |
| | CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAAC TATTCA TGGAAAAGAA | 780 |
| | ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTGTCATTA TGATGGTGAC AGTGGTGGCT | 840 |
| 30 | CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT | 900 |
| | TTTGAAAAGG AATATGATGA TGTCACAATC AAGATGATTT TTGCTATCGT GCAAATTATT | 960 |

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GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AAACCTTCAAA 1020
 AAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA 1080
 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTTC CCTCAGAGAG 1140
 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG 1200
 5 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA 1260
 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTA 1296

(41) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 431 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

15 Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg
 1 5 10 15
 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
 20 20 25 30
 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu
 20 35 40 45
 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
 50 55 60
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
 65 70 75 80
 25 Asn Ile Phe Ile Cys Ser Leu Ala Leu Ser Asp Leu Leu Ile Thr Phe
 85 90 95
 Phe Cys Ile Pro Val Thr Met Leu Gln Asn Ile Ser Asp Asn Trp Leu
 100 105 110
 Gly Gly Ala Phe Ile Cys Lys Met Val Pro Phe Val Gln Ser Thr Ala
 30 115 120 125
 Val Val Thr Glu Met Leu Thr Met Thr Cys Ile Ala Val Glu Arg His
 130 135 140
 Gln Gly Leu Val His Pro Phe Lys Met Lys Trp Gln Tyr Thr Asn Arg
 145 150 155 160

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Arg | Ala | Phe | Thr | Met | Leu | Gly | Val | Val | Trp | Leu | Val | Ala | Val | Ile | Val | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| | Gly | Ser | Pro | Met | Trp | His | Val | Gln | Gln | Leu | Glu | Ile | Lys | Tyr | Asp | Phe | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| 5 | Leu | Tyr | Glu | Lys | Glu | His | Ile | Cys | Cys | Leu | Glu | Glu | Trp | Thr | Ser | Pro | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| | Val | His | Gln | Lys | Ile | Tyr | Thr | Thr | Phe | Ile | Leu | Val | Ile | Leu | Phe | Leu | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| 10 | Leu | Pro | Leu | Met | Val | Met | Leu | Ile | Leu | Tyr | Ser | Lys | Ile | Gly | Tyr | Glu | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Leu | Trp | Ile | Lys | Lys | Arg | Val | Gly | Asp | Gly | Ser | Val | Leu | Arg | Thr | Ile | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| | His | Gly | Lys | Glu | Met | Ser | Lys | Ile | Ala | Arg | Lys | Lys | Lys | Arg | Ala | Val | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| 15 | Ile | Met | Met | Val | Thr | Val | Val | Ala | Leu | Phe | Ala | Val | Cys | Trp | Ala | Pro | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| | Phe | His | Val | Val | His | Met | Met | Ile | Glu | Tyr | Ser | Asn | Phe | Glu | Lys | Glu | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| 20 | Tyr | Asp | Asp | Val | Thr | Ile | Lys | Met | Ile | Phe | Ala | Ile | Val | Gln | Ile | Ile | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Gly | Phe | Ser | Asn | Ser | Ile | Cys | Asn | Pro | Ile | Val | Tyr | Ala | Phe | Met | Asn | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| | Glu | Asn | Phe | Lys | Lys | Asn | Val | Leu | Ser | Ala | Val | Cys | Tyr | Cys | Ile | Val | |
| | | | | 340 | | | | 345 | | | | | 350 | | | | |
| 25 | Asn | Lys | Thr | Phe | Ser | Pro | Ala | Gln | Arg | His | Gly | Asn | Ser | Gly | Ile | Thr | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| | Met | Met | Arg | Lys | Lys | Ala | Lys | Phe | Ser | Leu | Arg | Glu | Asn | Pro | Val | Glu | |
| | | 370 | | | | | 375 | | | | | 380 | | | | | |
| 30 | Glu | Thr | Lys | Gly | Glu | Ala | Phe | Ser | Asp | Gly | Asn | Ile | Glu | Val | Lys | Leu | |
| | 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| | Cys | Glu | Gln | Thr | Glu | Glu | Lys | Lys | Lys | Leu | Lys | Arg | His | Leu | Ala | Leu | |
| | | | | | 405 | | | | | 410 | | | | | 415 | | |
| | Phe | Arg | Ser | Glu | Leu | Ala | Glu | Asn | Ser | Pro | Leu | Asp | Ser | Gly | His | | |
| | | | | 420 | | | | 425 | | | | | | 430 | | | |

35 (42) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 24 base pairs

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- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

CTGTGTACAG CAGTTCGCAG AGTG

24

(43) INFORMATION FOR SEQ ID NO:42:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 24 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

15 GAGTGCCAGG CAGAGCAGGT AGAC

24

(44) INFORMATION FOR SEQ ID NO:43:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

25 CCCGAATTCC TGCTTGCTCC CAGCTTGGCC C

31

(45) INFORMATION FOR SEQ ID NO:44:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 32 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

TGTGGATCCT GCTGTCAAAG GTCCCATTCG GG

32

(46) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

TCACAATGCT AGGTGTGGTC

20

(47) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

TGCATAGACA ATGGGATTAC AG

22

(48) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 511 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

TCACAATGCT AGGTGTGGTC TGGCTGGTGG CAGTCATCGT AGGATCACCC ATGTGGCACC

60

TGCAACAACCT TGAGATCAAA TATGACTTCC TATATGAAAA GGAACACATC TGCTGCTTAG

120

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AAGAGTGGAC CAGCCCTGTG CACCAGAAGA TCTACACCAC CTCATCCTT GTCATCCTCT 180
TCCTCCTGCC TCTTATGGTG ATGCTTATTC TGTACGTAAA ATTGGTTATG AACTTTGGAT 240
AAAGAAAAGA GTTGGGGATG GTTCAGTGCT TCGAACTATT CATGGAAAAG AAATGTCCAA 300
AATAGCCAGG AAGAAGAAAC GAGCTGTCAT TATGATGGTG ACAGTGGTGG CTCTCTTTGC 360
5 TGTGTGCTGG GCACCATTC C ATGTTGTCCA TATGATGATT GAATACAGTA ATTTTGAAAA 420
GGAATATGAT GATGTCACAA TCAAGATGAT TTTTGCTATC GTGCAAATTA TTGGATTTTC 480
CAACTCCATC TGTAATCCCA TTGTCTATGC A 511

(49) INFORMATION FOR SEQ ID NO:48:

- (i) SEQUENCE CHARACTERISTICS:
10 (A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

CTGCTTAGAA GAGTGGACCA G 21

(50) INFORMATION FOR SEQ ID NO:49:

- (i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CTGTGCACCA GAAGATCTAC AC 22

(51) INFORMATION FOR SEQ ID NO:50:

- (i) SEQUENCE CHARACTERISTICS:
30 (A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

CAAGGATGAA GGTGGTGTAG A

21

5 (52) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

GTGTAGATCT TCTGGTGCAC AGG

23

15 (53) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GCAATGCAGG TCATAGTGAG C

21

(54) INFORMATION FOR SEQ ID NO:53:

25 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: YES

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

TGGAGCATGG TGACGGGAAT GCAGAAG

27

(55) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

GTGATGAGCA GGTCACTGAG CGCCAAG

27

(56) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

GCAATGCAGG CGCTTAACAT TAC

23

(57) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 22 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

30 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

TTGGGTTACA ATCTGAAGGG CA

22

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(58) INFORMATION FOR SEQ ID NO:57:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

10 ACTCCGTGTC CAGCAGGACT CTG

23

(58) INFORMATION FOR SEQ ID NO:58:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

20 TGCCTGTTCC TGGACCCTCA CGTG

24

(58) INFORMATION FOR SEQ ID NO:59:

- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

30 CAGGCCTTGG ATTTTAATGT CAGGGATGG

29

(61) INFORMATION FOR SEQ ID NO:60:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs

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- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GGAGAGTCAG CTCTGAAAGA ATTCAGG

27

(62) INFORMATION FOR SEQ ID NO:61:

- 10 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

15 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

TGATGTGATG CCAGATACTA ATAGCAC

27

(63) INFORMATION FOR SEQ ID NO:62:

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

CCTGATTCAT TTAGGTGAGA TTGAGAC

27

(64) INFORMATION FOR SEQ ID NO:63:

- 30 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 26 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

CCCAAGCTTC CCCAGGTGTA TTTGAT

26

(3) INFORMATION FOR SEQ ID NO:63:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GTTGGATCCA CATAATGCAT TTTCTC

26

(66) INFORMATION FOR SEQ ID NO:65:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60

GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120

GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180

ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240

25 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300

TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCACG 360

TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420

ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGTCG TGCTGGCAGG CTTGGCCAGT 480

TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540

30 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600

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ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660
 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720
 ATAATTATGG CAATTGTGCT TTTCTTTTTC TTTTCCTGGA TTCCCCACCA AATATTCACT 780
 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840
 5 GACACGGCCA TGCCTATCAC CATTGTGATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900
 TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960
 CCCCCAAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCACGCT TTCCTACCGC 1020
 CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

(67) INFORMATION FOR SEQ ID NO:66:

- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 359 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

- 15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Met | Ile | Leu | Asn | Ser | Ser | Thr | Glu | Asp | Gly | Ile | Lys | Arg | Ile | Gln | Asp | |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | | |
| | Asp | Cys | Pro | Lys | Ala | Gly | Arg | His | Asn | Tyr | Ile | Phe | Val | Met | Ile | Pro | |
| 20 | | | | 20 | | | | | 25 | | | | | 30 | | | |
| | Thr | Leu | Tyr | Ser | Ile | Ile | Phe | Val | Val | Gly | Ile | Phe | Gly | Asn | Ser | Leu | |
| | | | | 35 | | | | 40 | | | | | 45 | | | | |
| | Val | Val | Ile | Val | Ile | Tyr | Phe | Tyr | Met | Lys | Leu | Lys | Thr | Val | Ala | Ser | |
| | | | | 50 | | | 55 | | | | | 60 | | | | | |
| 25 | Val | Phe | Leu | Leu | Asn | Leu | Ala | Leu | Ala | Asp | Leu | Cys | Phe | Leu | Leu | Thr | |
| | 65 | | | | 70 | | | | | 75 | | | | | | 80 | |
| | Leu | Pro | Leu | Trp | Ala | Val | Tyr | Thr | Ala | Met | Glu | Tyr | Arg | Trp | Pro | Phe | |
| | | | | 85 | | | | | 90 | | | | | | 95 | | |
| | Gly | Asn | Tyr | Leu | Cys | Lys | Ile | Ala | Ser | Ala | Ser | Val | Ser | Phe | Asn | Leu | |
| 30 | | | | 100 | | | | 105 | | | | | | 110 | | | |
| | Tyr | Ala | Ser | Val | Phe | Leu | Leu | Thr | Cys | Leu | Ser | Ile | Asp | Arg | Tyr | Leu | |
| | | | | 115 | | | | 120 | | | | | 125 | | | | |
| | Ala | Ile | Val | His | Pro | Met | Lys | Ser | Arg | Leu | Arg | Arg | Thr | Met | Leu | Val | |

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| | 130 | | 135 | | 140 |
|----|---|-----|-----|-----|---------|
| | Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser | | | | |
| | 145 | | 150 | | 155 160 |
| 5 | Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn | | | | |
| | | 165 | | 170 | 175 |
| | Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro | | | | |
| | | 180 | | 185 | 190 |
| | Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe | | | | |
| | | 195 | | 200 | 205 |
| 10 | Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys | | | | |
| | | 210 | | 215 | 220 |
| | Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Lys | | | | |
| | | 225 | | 230 | 235 240 |
| 15 | Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His | | | | |
| | | 245 | | 250 | 255 |
| | Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg | | | | |
| | | 260 | | 265 | 270 |
| | Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile | | | | |
| | | 275 | | 280 | 285 |
| 20 | Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe | | | | |
| | | 290 | | 295 | 300 |
| | Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile | | | | |
| | | 305 | | 310 | 315 320 |
| 25 | Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr | | | | |
| | | 325 | | 330 | 335 |
| | Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro | | | | |
| | | 340 | | 345 | 350 |
| | Ala Pro Cys Phe Glu Val Glu | | | | |
| | | 355 | | | |

30 (68) INFORMATION FOR SEQ ID NO:67:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 27 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: DNA (genomic)

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

ACCATGGGCA GCCCCTGGAA CGGCAGC

27

(69) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

AGAACCACCA CCAGCAGGAC GCGGACGGTC TGCCGGTGG

39

(70) INFORMATION FOR SEQ ID NO:69:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

20 GTCCGCGTCC TGCTGGTGGT GGTTCTGGCA TTTATAATT

39

(71) INFORMATION FOR SEQ ID NO:70:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

CCTGGATCCT TATCCCATCG TCTTCACGTT AGC

33

30 (72) INFORMATION FOR SEQ ID NO:71:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

5 CTGGAATTCT CCTGCCAGCA TGGTGA
26

(73) INFORMATION FOR SEQ ID NO:72:

(i) SEQUENCE CHARACTERISTICS:

10 (A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

GCAGGATCCT ATATTGCGTG CTCTGTCCCC
30

(74) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

20 (A) LENGTH: 999 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

ATGGTGAACT CCACCCACCG TGGGATGCAC ACTTCTCTGC ACCTCTGGAA CCGCAGCAGT 60
TACAGACTGC ACAGCAATGC CAGTGAGTCC CTTGGAAAAG GCTACTCTGA TGGAGGGTGC 120
TACGAGCAAC TTTTGTCTC TCCTGAGGTG TTTGTGACTC TGGGTGTCAT CAGCTTGTTG 180
GAGAATATCT TAGTGATTGT GGCAATAGCC AAGAACAAGA ATCTGCATTC ACCCATGTAC 240
30 TTTTTCATCT GCAGCTTGGC TGTGGCTGAT ATGCTGGTGA GCGTTTCAAA TGGATCAGAA 300
ACCATATCA TCACCCTATT AAACAGTACA GATACGGATG CACAGAGTTT CACAGTGAAT 360
ATTGATAATG TCATTGACTC GGTGATCTGT AGCTCCTTGC TTGCATCCAT TTGCAGCCTG 420

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CTTTCAATTG CAGTGGACAG GTACTTTACT ATCTTCTATG CTCTCCAGTA CCATAACATT 480
 ATGACAGTTA AGCGGGTTGG GATCAGCATA AGTTGTATCT GGCAGCTTG CACGGTTTCA 540
 GGCATTTTGT TCATCATTTA CTCAGATAGT AGTGCTGTCA TCATCTGCCT CATCACCATG 600
 TTCTTCACCA TGCTGGCTCT CATGGCTTCT CTCTATGTCC ACATGTTTCCT GATGGCCAGG 660
 5 CTTCACATTA AGAGGATTGC TGTCTCCCC GGCCTGGTG CCATCCGCCA AGGTGCCAAT 720
 ATGAAGGGAG CGATTACCTT GACCATCCTG ATTGGCGTCT TTGTTGTCTG CTGGGCCCCA 780
 TTCTTCCTCC ACTTAATATT CTACATCTCT TGTCTCAGA ATCCATATTG TGTGTGCTTC 840
 ATGTCTCACT TTAACCTGTA TCTCATACTG ATCATGTGTA ATTCAATCAT CGATCCTCTG 900
 ATTTATGCAC TCCGGAGTCA AGAACTGAGG AAAACCTTCA AAGAGATCAT CTGTTGCTAT 960
 10 CCCCTGGGAG GCCTTTGTGA CTTGTCTAGC AGATATTAA 999

(75) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 332 amino acids
 (B) TYPE: amino acid
 15 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Met Val Asn Ser Thr His Arg Gly Met His Thr Ser Leu His Leu Trp
 20 1 5 10 15
 Asn Arg Ser Ser Tyr Arg Leu His Ser Asn Ala Ser Glu Ser Leu Gly
 20 25 30
 Lys Gly Tyr Ser Asp Gly Gly Cys Tyr Glu Gln Leu Phe Val Ser Pro
 35 40 45
 25 Glu Val Phe Val Thr Leu Gly Val Ile Ser Leu Leu Glu Asn Ile Leu
 50 55 60
 Val Ile Val Ala Ile Ala Lys Asn Lys Asn Leu His Ser Pro Met Tyr
 65 70 75 80
 Phe Phe Ile Cys Ser Leu Ala Val Ala Asp Met Leu Val Ser Val Ser
 30 85 90 95
 Asn Gly Ser Glu Thr Ile Ile Ile Thr Leu Leu Asn Ser Thr Asp Thr
 100 105 110
 Asp Ala Gln Ser Phe Thr Val Asn Ile Asp Asn Val Ile Asp Ser Val

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| | 115 | 120 | 125 |
|----|-------------------------|---------------------|---------------------|
| | Ile Cys Ser Ser Leu Leu | Ala Ser Ile Cys Ser | Leu Leu Ser Ile Ala |
| | 130 | 135 | 140 |
| 5 | Val Asp Arg Tyr Phe Thr | Ile Phe Tyr Ala Leu | Gln Tyr His Asn Ile |
| | 145 | 150 | 155 160 |
| | Met Thr Val Lys Arg Val | Gly Ile Ser Ile Ser | Cys Ile Trp Ala Ala |
| | | 165 | 170 175 |
| | Cys Thr Val Ser Gly Ile | Leu Phe Ile Ile Tyr | Ser Asp Ser Ser Ala |
| | | 180 | 185 190 |
| 10 | Val Ile Ile Cys Leu Ile | Thr Met Phe Phe Thr | Met Leu Ala Leu Met |
| | | 195 | 200 205 |
| | Ala Ser Leu Tyr Val His | Met Phe Leu Met Ala | Arg Leu His Ile Lys |
| | | 210 | 215 220 |
| 15 | Arg Ile Ala Val Leu Pro | Gly Thr Gly Ala Ile | Arg Gln Gly Ala Asn |
| | | 225 | 230 235 240 |
| | Met Lys Gly Ala Ile Thr | Leu Thr Ile Leu Ile | Gly Val Phe Val Val |
| | | 245 | 250 255 |
| | Cys Trp Ala Pro Phe Phe | Leu His Leu Ile Phe | Tyr Ile Ser Cys Pro |
| | | 260 | 265 270 |
| 20 | Gln Asn Pro Tyr Cys Val | Cys Phe Met Ser His | Phe Asn Leu Tyr Leu |
| | | 275 | 280 285 |
| | Ile Leu Ile Met Cys Asn | Ser Ile Ile Asp Pro | Leu Ile Tyr Ala Leu |
| | | 290 | 295 300 |
| 25 | Arg Ser Gln Glu Leu Arg | Lys Thr Phe Lys Glu | Ile Ile Cys Cys Tyr |
| | | 305 | 310 315 320 |
| | Pro Leu Gly Gly Leu Cys | Asp Leu Ser Ser Arg | Tyr |
| | | 325 | 330 |

(76) INFORMATION FOR SEQ ID NO:75:

30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 32 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

CCGAAGCTTC GAGCTGAGTA AGGCGGCGGG CT

32

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(77) INFORMATION FOR SEQ ID NO:76:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

GTGGAATTCA TTTGCCCTGC CTCAACCCCC A 31

10 (78) INFORMATION FOR SEQ ID NO:77:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1344 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC 60
 CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG 120
 20 CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT 180
 TACGCAGTGA TCTTCCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTGGGA 240
 CTGAGCCGCC GCCTGAGGAC TGTCACCAAT GCCTTCCTCC TCTCACTGGC AGTCAGCGAC 300
 CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC 360
 ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG 420
 25 TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG 480
 CAGGCACGAG TGTGGCAGAC GCGCTCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG 540
 CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT 600
 CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA 660
 CTGCTGCTTC TGCTCTTGTT CTTTCATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT 720
 30 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA 780
 AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG 840

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CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC      900
CGGCCTGCCC TGGAGCTGAC GCGCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC      960
ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGGTGCGAA TGTGCTGGT GATCGTTGTG      1020
CTTTTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC      1080
5  CCGGGTGCAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACTT GCTGAGCTAC      1140
GCCTCGGCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC      1200
TGCCTGGAAG CTTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT      1260
CCCGATGAGG ACCCTCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC      1320
ATCAGCACAC TGGGCCCTGG CTGA                                          1344

```

10 (79) INFORMATION FOR SEQ ID NO:78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 447 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

15 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

```

Met Glu Leu Leu Lys Leu Asn Arg Ser Val Gln Gly Thr Gly Pro Gly
1           5           10           15
20  Pro Gly Ala Ser Leu Cys Arg Pro Gly Ala Pro Leu Leu Asn Ser Ser
           20           25           30
Ser Val Gly Asn Leu Ser Cys Glu Pro Pro Arg Ile Arg Gly Ala Gly
           35           40           45
25  Thr Arg Glu Leu Glu Leu Ala Ile Arg Ile Thr Leu Tyr Ala Val Ile
           50           55           60
Phe Leu Met Ser Val Gly Gly Asn Met Leu Ile Ile Val Val Leu Gly
65           70           75           80
Leu Ser Arg Arg Leu Arg Thr Val Thr Asn Ala Phe Leu Leu Ser Leu
           85           90           95
30  Ala Val Ser Asp Leu Leu Leu Ala Val Ala Cys Met Pro Phe Thr Leu
           100          105          110
Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys
           115          120          125

```


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| | | |
|----|---|-----------------|
| | Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser | |
| | 130 | 135 140 |
| | Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu | |
| | 145 | 150 155 160 |
| 5 | Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val | |
| | | 165 170 175 |
| | Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr | |
| | | 180 185 190 |
| 10 | Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg | |
| | | 195 200 205 |
| | Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu | |
| | | 210 215 220 |
| | Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu | |
| | | 225 230 235 240 |
| 15 | Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp | |
| | | 245 250 255 |
| | Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala | |
| | | 260 265 270 |
| 20 | Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys | |
| | | 275 280 285 |
| | Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu | |
| | | 290 295 300 |
| | Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro | |
| | | 305 310 315 320 |
| 25 | Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Val Arg Met Leu Leu | |
| | | 325 330 335 |
| | Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala | |
| | | 340 345 350 |
| 30 | Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser | |
| | | 355 360 365 |
| | Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys | |
| | | 370 375 380 |
| | Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala | |
| | | 385 390 395 400 |
| 35 | Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg | |
| | | 405 410 415 |
| | Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser | |

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420

425

430

Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly
 435 440 445

(80) INFORMATION FOR SEQ ID NO:79:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

TGCAAGCTTA AAAAGGAAAA AATGAACAGC 30

(81) INFORMATION FOR SEQ ID NO:80:

- 15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

TAAGGATCCC TTCCCTTCAA AACATCCTTG 30

(82) INFORMATION FOR SEQ ID NO:81:

- 25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1014 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

30 ATGAACAGCA CATGTATTGA AGAACAGCAT GACCTGGATC ACTATTTGTT TCCCATTTGTT 60
 TACATCTTTG TGATTATAGT CAGCATTCCA GCCAATATTG GATCTCTGTG TGTGTCTTTC 120
 CTGCAACCCA AGAAGGAAAG TGAAGTAGGA ATTTACCTCT TCAGTTTGTC ACTATCAGAT 180
 TTACTCTATG CATTAAGTCT CCCTTTATGG ATTGATTATA CTTGGAATAA AGACAACTGG 240

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ACTTTCTCTC CTGCCTTGTG CAAAGGGAGT GCTTTTCTCA TGTACATGAA GTTTTACAGC 300
 AGCACAGCAT TCCTCACCTG CATTGCCGTT GATCGGTATT TGGCTGTTGT CTACCCTTTG 360
 AAGTTTTTTT TCCTAAGGAC AAGAAGAATT GCACTCATGG TCAGCCTGTC CATCTGGATA 420
 TTGGAAACCA TCTTCAATGC TGTCAATGTTG TGGGAAGATG AAACAGTTGT TGAATATTGC 480
 5 GATGCCGAAA AGTCTAATTT TACTTTATGC TATGACAAAT ACCCTTTAGA GAAATGGCAA 540
 ATCAACCTCA ACTTGTTTCAG GACGTGTACA GGCTATGCAA TACCTTTGGT CACCATCCTG 600
 ATCTGTAACC GGAAAGTCTA CCAAGCTGTG CGGCACAATA AAGCCACGGA AAACAAGGAA 660
 AAGAAGAGAA TCATAAACT ACTTGTCAGC ATCACAGTTA CTTTTGTCTT ATGCTTTACT 720
 CCCTTTCATG TGATGTTGCT GATTCGCTGC ATTTTAGAGC ATGCTGTGAA CTTCGAAGAC 780
 10 CACAGCAATT CTGGGAAGCG AACTTACACA ATGTATAGAA TCACGGTTGC ATTAACAAGT 840
 TTAAATTGTG TTGCTGATCC AATTCTGTAC TGT'TTTGTTA CCGAAACAGG AAGATATGAT 900
 ATGTGGAATA TATTAAAATT CTGCACTGGG AGGTGTAATA CATCACAAAG ACAAAGAAAA 960
 CGCATACTTT CTGTGTCTAC AAAAGATACT ATGGAATTAG AGGTCCTTGA GTAG 1014

(83) INFORMATION FOR SEQ ID NO:82:

- 15 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 337 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - (D) TOPOLOGY: not relevant

- 20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

Met Asn Ser Thr Cys Ile Glu Glu Gln His Asp Leu Asp His Tyr Leu
 1 5 10 15
 Phe Pro Ile Val Tyr Ile Phe Val Ile Ile Val Ser Ile Pro Ala Asn
 25 20 25 30
 Ile Gly Ser Leu Cys Val Ser Phe Leu Gln Pro Lys Lys Glu Ser Glu
 35 40 45
 Leu Gly Ile Tyr Leu Phe Ser Leu Ser Leu Ser Asp Leu Leu Tyr Ala
 50 55 60
 30 Leu Thr Leu Pro Leu Trp Ile Asp Tyr Thr Trp Asn Lys Asp Asn Trp
 65 70 75 80
 Thr Phe Ser Pro Ala Leu Cys Lys Gly Ser Ala Phe Leu Met Tyr Met

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| | 85 | 90 | 95 |
|----|---|-----|-----|
| | Lys Phe Tyr Ser Ser Thr Ala Phe Leu Thr Cys Ile Ala Val Asp Arg | | |
| | 100 | 105 | 110 |
| 5 | Tyr Leu Ala Val Val Tyr Pro Leu Lys Phe Phe Phe Leu Arg Thr Arg | | |
| | 115 | 120 | 125 |
| | Arg Ile Ala Leu Met Val Ser Leu Ser Ile Trp Ile Leu Glu Thr Ile | | |
| | 130 | 135 | 140 |
| | Phe Asn Ala Val Met Leu Trp Glu Asp Glu Thr Val Val Glu Tyr Cys | | |
| | 145 | 150 | 155 |
| 10 | Asp Ala Glu Lys Ser Asn Phe Thr Leu Cys Tyr Asp Lys Tyr Pro Leu | | |
| | 165 | 170 | 175 |
| | Glu Lys Trp Gln Ile Asn Leu Asn Leu Phe Arg Thr Cys Thr Gly Tyr | | |
| | 180 | 185 | 190 |
| 15 | Ala Ile Pro Leu Val Thr Ile Leu Ile Cys Asn Arg Lys Val Tyr Gln | | |
| | 195 | 200 | 205 |
| | Ala Val Arg His Asn Lys Ala Thr Glu Asn Lys Glu Lys Lys Arg Ile | | |
| | 210 | 215 | 220 |
| | Ile Lys Leu Leu Val Ser Ile Thr Val Thr Phe Val Leu Cys Phe Thr | | |
| | 225 | 230 | 235 |
| 20 | Pro Phe His Val Met Leu Leu Ile Arg Cys Ile Leu Glu His Ala Val | | |
| | 245 | 250 | 255 |
| | Asn Phe Glu Asp His Ser Asn Ser Gly Lys Arg Thr Tyr Thr Met Tyr | | |
| | 260 | 265 | 270 |
| 25 | Arg Ile Thr Val Ala Leu Thr Ser Leu Asn Cys Val Ala Asp Pro Ile | | |
| | 275 | 280 | 285 |
| | Leu Tyr Cys Phe Val Thr Glu Thr Gly Arg Tyr Asp Met Trp Asn Ile | | |
| | 290 | 295 | 300 |
| | Leu Lys Phe Cys Thr Gly Arg Cys Asn Thr Ser Gln Arg Gln Arg Lys | | |
| | 305 | 310 | 315 |
| 30 | Arg Ile Leu Ser Val Ser Thr Lys Asp Thr Met Glu Leu Glu Val Leu | | |
| | 325 | 330 | 335 |
| | Glu | | |

(84) INFORMATION FOR SEQ ID NO:83:

- 35 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 40 base pairs
 - (B) TYPE: nucleic acid

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- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

5 CAGGAAGAAG AAACGAGCTG TCATTATGAT GGTGACAGTG
40

(85) INFORMATION FOR SEQ ID NO:84:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 40 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

15 CACTGTCACC ATCATAATGA CAGCTCGTTT CTTCTTCCTG
40

(86) INFORMATION FOR SEQ ID NO:85:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 30 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

25 GGCCACCGGC AGACCAAACG CGTCCTGCTG
30

(87) INFORMATION FOR SEQ ID NO:86:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 31 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

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CTCCTTCGGT CTCCTATCG TTGTCAGAAG T
31

(88) INFORMATION FOR SEQ ID NO:87:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

GGAAAAGAAG AGAATCAAAA AACTACTTGT CAGCATC 37

(89) INFORMATION FOR SEQ ID NO:88:

- 15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

20 CTCCTTCGGT CTCCTATCG TTGTCAGAAG T 31

(90) INFORMATION FOR SEQ ID NO:89:

- 25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60

30 GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120

GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180

ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240

TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300

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| | | | | | | | |
|----|------------|------------|------------|------------|------------|-------------|------|
| | TGTAAGATTG | CTTCAGCCAG | CGTCAGTTTC | AACCTGTACG | CTAGTGTGTT | TCTACTCACG | 360 |
| | TGTCTCAGCA | TTGATCGATA | CCTGGCTATT | GTTCACCCAA | TGAAGTCCCG | CCTTCGACGC | 420 |
| | ACAATGCTTG | TAGCCAAAGT | CACCTGCATC | ATCATTTGGC | TGCTGGCAGG | CTTGGCCAGT | 480 |
| | TTGCCAGCTA | TAATCCATCG | AAATGTATTT | TTCATTGAGA | ACACCAATAT | TACAGTTTGT | 540 |
| 5 | GCTTTCCATT | ATGAGTCCCA | AAATTCAACC | CTTCCGATAG | GGCTGGGCCT | GACCAAAAAT | 600 |
| | ATACTGGGTT | TCCTGTTTCC | TTTTCTGATC | ATTCTTACAA | GTTATACTCT | TATTTGGAAG | 660 |
| | GCCCTAAAGA | AGGCTTATGA | AATTCAGAAG | AACAAACCAA | GAAATGATGA | TATTA AAAAG | 720 |
| | ATAATTATGG | CAATTGTGCT | TTTCTTTTTC | TTTTCTTGGA | TTCCCCACCA | AATATTCACT | 780 |
| | TTTCTGGATG | TATTGATTCA | ACTAGGCATC | ATACGTGACT | GTAGAATTGC | AGATATTGTG | 840 |
| 10 | GACACGGCCA | TGCCTATCAC | CATTTGTATA | GCTTATTTTA | ACAATTGCCT | GAATCCTCTT | 900 |
| | TTTTATGGCT | TTCTGGGGAA | AAAATTTAAA | AGATATTTTC | TCCAGCTTCT | AAAATATATT | 960 |
| | CCCCCAAAG | CCAAATCCCA | CTCAAACCTT | TCAACAAAAA | TGAGCACGCT | TTCCTACCGC | 1020 |
| | CCCTCAGATA | ATGTAAGCTC | ATCCACCAAG | AAGCCTGCAC | CATGTTTTGA | GGTTGAGTGA | 1080 |

(91) INFORMATION FOR SEQ ID NO:90:

15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 359 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

| | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | Met | Ile | Leu | Asn | Ser | Ser | Thr | Glu | Asp | Gly | Ile | Lys | Arg | Ile | Gln | Asp |
| | 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| 25 | Asp | Cys | Pro | Lys | Ala | Gly | Arg | His | Asn | Tyr | Ile | Phe | Val | Met | Ile | Pro |
| | | | | 20 | | | | | 25 | | | | | 30 | | |
| | Thr | Leu | Tyr | Ser | Ile | Ile | Phe | Val | Val | Gly | Ile | Phe | Gly | Asn | Ser | Leu |
| | | | 35 | | | | | 40 | | | | | 45 | | | |
| | Val | Val | Ile | Val | Ile | Tyr | Phe | Tyr | Met | Lys | Leu | Lys | Thr | Val | Ala | Ser |
| | | 50 | | | | | 55 | | | | | 60 | | | | |
| 30 | Val | Phe | Leu | Leu | Asn | Leu | Ala | Leu | Ala | Asp | Leu | Cys | Phe | Leu | Leu | Thr |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| | Leu | Pro | Leu | Trp | Ala | Val | Tyr | Thr | Ala | Met | Glu | Tyr | Arg | Trp | Pro | Phe |

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| | 85 | 90 | 95 |
|----|---|-----|-----|
| | Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn Leu | | |
| | 100 | 105 | 110 |
| 5 | Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu | | |
| | 115 | 120 | 125 |
| | Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val | | |
| | 130 | 135 | 140 |
| | Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser | | |
| | 145 | 150 | 155 |
| 10 | Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn | | |
| | 165 | 170 | 175 |
| | Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro | | |
| | 180 | 185 | 190 |
| 15 | Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe | | |
| | 195 | 200 | 205 |
| | Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys | | |
| | 210 | 215 | 220 |
| | Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Lys Lys | | |
| | 225 | 230 | 235 |
| 20 | Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His | | |
| | 245 | 250 | 255 |
| | Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg | | |
| | 260 | 265 | 270 |
| 25 | Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile | | |
| | 275 | 280 | 285 |
| | Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe | | |
| | 290 | 295 | 300 |
| | Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile | | |
| | 305 | 310 | 315 |
| 30 | Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr | | |
| | 325 | 330 | 335 |
| | Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro | | |
| | 340 | 345 | 350 |
| 35 | Ala Pro Cys Phe Glu Val Glu | | |
| | 355 | | |

(92) INFORMATION FOR SEQ ID NO:91:

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- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

CCAAGAAATG ATGATATTAA AAAGATAATT ATGGC

35

(93) INFORMATION FOR SEQ ID NO:92:

- 10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T

31

(94) INFORMATION FOR SEQ ID NO:93:

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

| | |
|--|-----|
| ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA | 60 |
| GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG | 120 |
| GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG | 180 |
| ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT | 240 |
| 30 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA | 300 |
| TGTAAGATTG CTTCAGCCAG CGTCAGTTTC GCCCTGTACG CTAGTGTGTT TCTACTCACG | 360 |
| TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC | 420 |

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ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGGC TGCTGGCAGG CTTGGCCAGT 480
 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540
 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600
 ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660
 5 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720
 ATAATTATGG CAATTGTGCT TTTCTTTTTT TTTTCTGGA TTCCCCACCA AATATTCACT 780
 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840
 GACACGGCCA TGCCTATCAC CATTTGTATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900
 TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960
 10 CCCCCAAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCAGCTT TTCCTACCGC 1020
 CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTGAGTGA 1080

(95) INFORMATION FOR SEQ ID NO:94:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 359 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

20 Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp
 1 5 10 15
 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro
 20 25 30
 25 Thr Leu Tyr Ser Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu
 35 40 45
 Val Val Ile Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser
 50 55 60
 Val Phe Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr
 65 70 75 80
 30 Leu Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe
 85 90 95
 Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Ala Leu

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| | 100 | 105 | 110 |
|----|---|-----|-----|
| | Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg Tyr Leu | | |
| | 115 | 120 | 125 |
| 5 | Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr Met Leu Val | | |
| | 130 | 135 | 140 |
| | Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala Gly Leu Ala Ser | | |
| | 145 | 150 | 155 |
| | Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe Ile Glu Asn Thr Asn | | |
| | | 165 | 170 |
| 10 | Ile Thr Val Cys Ala Phe His Tyr Glu Ser Gln Asn Ser Thr Leu Pro | | |
| | | 180 | 185 |
| | Ile Gly Leu Gly Leu Thr Lys Asn Ile Leu Gly Phe Leu Phe Pro Phe | | |
| | | 195 | 200 |
| 15 | Leu Ile Ile Leu Thr Ser Tyr Thr Leu Ile Trp Lys Ala Leu Lys Lys | | |
| | | 210 | 215 |
| | Ala Tyr Glu Ile Gln Lys Asn Lys Pro Arg Asn Asp Asp Ile Phe Lys | | |
| | | 225 | 230 |
| | Ile Ile Met Ala Ile Val Leu Phe Phe Phe Phe Ser Trp Ile Pro His | | |
| | | 245 | 250 |
| 20 | Gln Ile Phe Thr Phe Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg | | |
| | | 260 | 265 |
| | Asp Cys Arg Ile Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile | | |
| | | 275 | 280 |
| 25 | Cys Ile Ala Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe | | |
| | | 290 | 295 |
| | Leu Gly Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile | | |
| | | 305 | 310 |
| | Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr | | |
| | | 325 | 330 |
| 30 | Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys Pro | | |
| | | 340 | 345 |
| | Ala Pro Cys Phe Glu Val Glu | | |
| | | 355 | |

(97) INFORMATION FOR SEQ ID NO:95:

- 35 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 26 base pairs
 - (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

CCCAAGCTTC CCCAGGTGTA TTTGAT

26

(97) INFORMATION FOR SEQ ID NO:96:

(i) SEQUENCE CHARACTERISTICS:

10

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

CCTGCAGGCG AAAGTGAATC TGGCTGAAG

29

(98) INFORMATION FOR SEQ ID NO:97:

(i) SEQUENCE CHARACTERISTICS:

20

(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:

CTGTACGCTA GTGTGTTTCT ACTCACGTGT CTCAGCATTG AT

42

(99) INFORMATION FOR SEQ ID NO:98:

(i) SEQUENCE CHARACTERISTICS:

30

(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:

GTTGGATCCA CATAATGCAT TTTCTC

26

(100) INFORMATION FOR SEQ ID NO:99:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1080 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:

ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAAA 60

GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120

GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180

15 ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240

TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300

TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCACG 360

TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420

ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGGC TGCTGGCAGG CTTGGCCAGT 480

20 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540

GCTTTCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600

ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATTTTGG AATTCGAAAA 660

CACTTACTGA AGACGAATAG CTATGGGAAG AACAGGATAA CCCGTGACCA AGTTAAGAAG 720

ATAATTATGG CAATTGTGCT TTTCTTTTTT TTTTCCTGGA TTCCCCACCA AATATTCACT 780

25 TTTCTGGATG TATTGATTCA ACTAGGCATC ATACGTGACT GTAGAATTGC AGATATTGTG 840

GACACGGCCA TGCCTATCAC CATTTGTATA GCTTATTTTA ACAATTGCCT GAATCCTCTT 900

TTTTATGGCT TTCTGGGGAA AAAATTTAAA AGATATTTTC TCCAGCTTCT AAAATATATT 960

CCCCCAAAG CCAAATCCCA CTCAAACCTT TCAACAAAAA TGAGCACGCT TTCCTACCGC 1020

CCCTCAGATA ATGTAAGCTC ATCCACCAAG AAGCCTGCAC CATGTTTTGA GGTTGAGTGA 1080

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(101) INFORMATION FOR SEQ ID NO:100:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 359 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:

| | | | | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 10 | Met | Ile | Leu | Asn | Ser | Ser | Thr | Glu | Asp | Gly | Ile | Lys | Arg | Ile | Gln | Asp | 1 | 5 | 10 | 15 |
| | Asp | Cys | Pro | Lys | Ala | Gly | Arg | His | Asn | Tyr | Ile | Phe | Val | Met | Ile | Pro | 20 | 25 | 30 | |
| | Thr | Leu | Tyr | Ser | Ile | Ile | Phe | Val | Val | Gly | Ile | Phe | Gly | Asn | Ser | Leu | 35 | 40 | 45 | |
| 15 | Val | Val | Ile | Val | Ile | Tyr | Phe | Tyr | Met | Lys | Leu | Lys | Thr | Val | Ala | Ser | 50 | 55 | 60 | |
| | Val | Phe | Leu | Leu | Asn | Leu | Ala | Leu | Ala | Asp | Leu | Cys | Phe | Leu | Leu | Thr | 65 | 70 | 75 | 80 |
| 20 | Leu | Pro | Leu | Trp | Ala | Val | Tyr | Thr | Ala | Met | Glu | Tyr | Arg | Trp | Pro | Phe | 85 | 90 | 95 | |
| | Gly | Asn | Tyr | Leu | Cys | Lys | Ile | Ala | Ser | Ala | Ser | Val | Ser | Phe | Asn | Leu | 100 | 105 | 110 | |
| | Tyr | Ala | Ser | Val | Phe | Leu | Leu | Thr | Cys | Leu | Ser | Ile | Asp | Arg | Tyr | Leu | 115 | 120 | 125 | |
| 25 | Ala | Ile | Val | His | Pro | Met | Lys | Ser | Arg | Leu | Arg | Arg | Thr | Met | Leu | Val | 130 | 135 | 140 | |
| | Ala | Lys | Val | Thr | Cys | Ile | Ile | Ile | Trp | Leu | Leu | Ala | Gly | Leu | Ala | Ser | 145 | 150 | 155 | 160 |
| 30 | Leu | Pro | Ala | Ile | Ile | His | Arg | Asn | Val | Phe | Phe | Ile | Glu | Asn | Thr | Asn | 165 | 170 | 175 | |
| | Ile | Thr | Val | Cys | Ala | Phe | His | Tyr | Glu | Ser | Gln | Asn | Ser | Thr | Leu | Pro | 180 | 185 | 190 | |
| | Ile | Gly | Leu | Gly | Leu | Thr | Lys | Asn | Ile | Leu | Gly | Phe | Leu | Phe | Pro | Phe | 195 | 200 | 205 | |
| 35 | Leu | Ile | Ile | Leu | Thr | Ser | Tyr | Phe | Gly | Ile | Arg | Lys | His | Leu | Leu | Lys | 210 | 215 | 220 | |

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Thr | Asn | Ser | Tyr | Gly | Lys | Asn | Arg | Ile | Thr | Arg | Asp | Gln | Val | Lys | Lys | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Ile | Ile | Met | Ala | Ile | Val | Leu | Phe | Phe | Phe | Phe | Ser | Trp | Ile | Pro | His | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 5 | Gln | Ile | Phe | Thr | Phe | Leu | Asp | Val | Leu | Ile | Gln | Leu | Gly | Ile | Ile | Arg | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Asp | Cys | Arg | Ile | Ala | Asp | Ile | Val | Asp | Thr | Ala | Met | Pro | Ile | Thr | Ile | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| 10 | Cys | Ile | Ala | Tyr | Phe | Asn | Asn | Cys | Leu | Asn | Pro | Leu | Phe | Tyr | Gly | Phe | |
| | 290 | | | | | 295 | | | | | | 300 | | | | | |
| | Leu | Gly | Lys | Lys | Phe | Lys | Arg | Tyr | Phe | Leu | Gln | Leu | Leu | Lys | Tyr | Ile | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Pro | Pro | Lys | Ala | Lys | Ser | His | Ser | Asn | Leu | Ser | Thr | Lys | Met | Ser | Thr | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| 15 | Leu | Ser | Tyr | Arg | Pro | Ser | Asp | Asn | Val | Ser | Ser | Ser | Thr | Lys | Lys | Pro | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| | Ala | Pro | Cys | Phe | Glu | Val | Glu | | | | | | | | | | |
| | | | | 355 | | | | | | | | | | | | | |

(102) INFORMATION FOR SEQ ID NO:101:

- 20 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 37 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:

TCCGAATTCC AAAATAACTT GTAAGAATGA TCAGAAA

37

(103) INFORMATION FOR SEQ ID NO:102:

- 30 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 35 (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:

AGATCTTAAG AAGATAATTA TGGCAATTGT GCT

33

(104) INFORMATION FOR SEQ ID NO:103:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:

AATTCGAAAA CACTTACTGA AGACGAATAG CTATGGGAAG AACAGGATAA CCCGTGACCA

60

AG

62

(105) INFORMATION FOR SEQ ID NO:104:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 62 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:

TTAACTTGGT CACGGGTTAT CCTGTTCTTC CCATAGCTAT TCGTCTTCAG TAAGTGTTTT

60

CG

62

25 (106) INFORMATION FOR SEQ ID NO:105:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 1083 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:105:

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ATGATTCTCA ACTCTTCTAC TGAAGATGGT ATTAAAAGAA TCCAAGATGA TTGTCCCAA 60
 GCTGGAAGGC ATAATTACAT ATTTGTCATG ATTCCTACTT TATACAGTAT CATCTTTGTG 120
 GTGGGAATAT TTGGAAACAG CTTGGTGGTG ATAGTCATTT ACTTTTATAT GAAGCTGAAG 180
 ACTGTGGCCA GTGTTTTTCT TTTGAATTTA GCACTGGCTG ACTTATGCTT TTTACTGACT 240
 5 TTGCCACTAT GGGCTGTCTA CACAGCTATG GAATACCGCT GGCCCTTTGG CAATTACCTA 300
 TGTAAGATTG CTTCAGCCAG CGTCAGTTTC AACCTGTACG CTAGTGTGTT TCTACTCACG 360
 TGTCTCAGCA TTGATCGATA CCTGGCTATT GTTCACCCAA TGAAGTCCCG CCTTCGACGC 420
 ACAATGCTTG TAGCCAAAGT CACCTGCATC ATCATTGTGGC TGCTGGCAGG CTTGGCCAGT 480
 TTGCCAGCTA TAATCCATCG AAATGTATTT TTCATTGAGA ACACCAATAT TACAGTTTGT 540
 10 GCTTTCCATT ATGAGTCCCA AAATTCAACC CTTCCGATAG GGCTGGGCCT GACCAAAAAT 600
 ATACTGGGTT TCCTGTTTCC TTTTCTGATC ATTCTTACAA GTTATACTCT TATTTGGAAG 660
 GCCCTAAAGA AGGCTTATGA AATTCAGAAG AACAAACCAA GAAATGATGA TATTTTAAAG 720
 ATAATTATGG CAGCAATTGT GCTTTTCTTT TTCTTTTCCT GGATTCCCCA CCAAATATTC 780
 ACTTTTCTGG ATGTATTGAT TCAACTAGGC ATCATACGTG ACTGTAGAAT TGCAGATATT 840
 15 GTGGACACGG CCATGCCTAT CACCATTGTG ATAGCTTATT TTAACAATTG CCTGAATCCT 900
 CTTTTTTATG GCTTTCTGGG GAAAAAATTT AAAAGATATT TTCTCCAGCT TCTAAAATAT 960
 ATTCCCCCAA AAGCCAAATC CCACTCAAAC CTTTCAACAA AAATGAGCAC GCTTTCCTAC 1020
 CGCCCCTCAG ATAATGTAAG CTCATCCACC AAGAAGCCTG CACCATGTTT TGAGGTTGAG 1080
 TGA 1083

20 (107) INFORMATION FOR SEQ ID NO:106:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 360 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS:
 - 25 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:

Met Ile Leu Asn Ser Ser Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp
 1 5 10 15

30 Asp Cys Pro Lys Ala Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro

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| | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | | | | | 20 | | | | | 25 | | | | | | 30 |
| | Thr | Leu | Tyr | Ser | Ile | Ile | Phe | Val | Val | Gly | Ile | Phe | Gly | Asn | Ser | Leu |
| | | | 35 | | | | | 40 | | | | | 45 | | | |
| 5 | Val | Val | Ile | Val | Ile | Tyr | Phe | Tyr | Met | Lys | Leu | Lys | Thr | Val | Ala | Ser |
| | | 50 | | | | | 55 | | | | | 60 | | | | |
| | Val | Phe | Leu | Leu | Asn | Leu | Ala | Leu | Ala | Asp | Leu | Cys | Phe | Leu | Leu | Thr |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| | Leu | Pro | Leu | Trp | Ala | Val | Tyr | Thr | Ala | Met | Glu | Tyr | Arg | Trp | Pro | Phe |
| | | | | | 85 | | | | | 90 | | | | | 95 | |
| 10 | Gly | Asn | Tyr | Leu | Cys | Lys | Ile | Ala | Ser | Ala | Ser | Val | Ser | Phe | Asn | Leu |
| | | | | 100 | | | | | 105 | | | | | 110 | | |
| | Tyr | Ala | Ser | Val | Phe | Leu | Leu | Thr | Cys | Leu | Ser | Ile | Asp | Arg | Tyr | Leu |
| | | | 115 | | | | | 120 | | | | | 125 | | | |
| 15 | Ala | Ile | Val | His | Pro | Met | Lys | Ser | Arg | Leu | Arg | Arg | Thr | Met | Leu | Val |
| | | 130 | | | | | 135 | | | | | | 140 | | | |
| | Ala | Lys | Val | Thr | Cys | Ile | Ile | Ile | Trp | Leu | Leu | Ala | Gly | Leu | Ala | Ser |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| | Leu | Pro | Ala | Ile | Ile | His | Arg | Asn | Val | Phe | Phe | Ile | Glu | Asn | Thr | Asn |
| | | | | | 165 | | | | | 170 | | | | | 175 | |
| 20 | Ile | Thr | Val | Cys | Ala | Phe | His | Tyr | Glu | Ser | Gln | Asn | Ser | Thr | Leu | Pro |
| | | | | 180 | | | | | 185 | | | | | 190 | | |
| | Ile | Gly | Leu | Gly | Leu | Thr | Lys | Asn | Ile | Leu | Gly | Phe | Leu | Phe | Pro | Phe |
| | | | 195 | | | | | 200 | | | | | 205 | | | |
| 25 | Leu | Ile | Ile | Leu | Thr | Ser | Tyr | Thr | Leu | Ile | Trp | Lys | Ala | Leu | Lys | Lys |
| | | 210 | | | | | 215 | | | | | 220 | | | | |
| | Ala | Tyr | Glu | Ile | Gln | Lys | Asn | Lys | Pro | Arg | Asn | Asp | Asp | Ile | Phe | Lys |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| | Ile | Ile | Met | Ala | Ala | Ile | Val | Leu | Phe | Phe | Phe | Phe | Ser | Trp | Ile | Pro |
| | | | | | 245 | | | | | 250 | | | | | 255 | |
| 30 | His | Gln | Ile | Phe | Thr | Phe | Leu | Asp | Val | Leu | Ile | Gln | Leu | Gly | Ile | Ile |
| | | | | 260 | | | | | 265 | | | | | 270 | | |
| | Arg | Asp | Cys | Arg | Ile | Ala | Asp | Ile | Val | Asp | Thr | Ala | Met | Pro | Ile | Thr |
| | | | 275 | | | | | 280 | | | | | 285 | | | |
| 35 | Ile | Cys | Ile | Ala | Tyr | Phe | Asn | Asn | Cys | Leu | Asn | Pro | Leu | Phe | Tyr | Gly |
| | | 290 | | | | | 295 | | | | | 300 | | | | |
| | Phe | Leu | Gly | Lys | Lys | Phe | Lys | Arg | Tyr | Phe | Leu | Gln | Leu | Leu | Lys | Tyr |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 |

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Ile Pro Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser
325 330 335

Thr Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
340 345 350

5 Pro Ala Pro Cys Phe Glu Val Glu
 355 360

(108) INFORMATION FOR SEQ ID NO:107:

10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:107:

CCCAAGCTTC CCCAGGTGTA TTTGAT 26

(109) INFORMATION FOR SEQ ID NO:108:

20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:108:

AAGCACAATT GCTGCATAAT TATCTTAAAA ATATCATC 38

(110) INFORMATION FOR SEQ ID NO:109:

30 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:109:

AAGATAATTA TGGCAGCAAT TGTGCTTTTC TTTTCTTT

39

(111) INFORMATION FOR SEQ ID NO:110:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 26 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

10 (iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:

GTTGGATCCA CATAATGCAT TTTCTC

26

(112) INFORMATION FOR SEQ ID NO:111:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 1344 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC 60

CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG 120

CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT 180

TACGCACTGA TCTTCCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTTGGGA 240

25 CTGAGCCGCC GCCTGAGGAC TGTCACCAAT GCCTTCCTCC TCTCACTGGC AGTCAGCGAC 300

CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC 360

ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG 420

TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG 480

CAGGCACGAG TGTGGCAGAC GCGCTCCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG 540

30 CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT 600

CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA 660

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CTGCTGCTTC TGCTCTTGTT CTTTCATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT 720
 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA 780
 AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG 840
 CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC 900
 5 CGGCCTGCCC TGGAGCTGAC GGCCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC 960
 ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGAAACGAA TGTGCTGGT GATCGTTGTG 1020
 CTTTTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC 1080
 CCGGGTGAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACTT GCTGAGCTAC 1140
 GCCTCGGCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC 1200
 10 TGCCTGGAAA CTTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT 1260
 CCCGATGAGG ACCCTCCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC 1320
 ATCAGCACAC TGGGCCCTGG CTGA 1344

(113) INFORMATION FOR SEQ ID NO:112:

- (i) SEQUENCE CHARACTERISTICS:
 15 (A) LENGTH: 447 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

- 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:112:

Met Glu Leu Leu Lys Leu Asn Arg Ser Val Gln Gly Thr Gly Pro Gly
 1 5 10 15
 Pro Gly Ala Ser Leu Cys Arg Pro Gly Ala Pro Leu Leu Asn Ser Ser
 20 25 30
 25 Ser Val Gly Asn Leu Ser Cys Glu Pro Pro Arg Ile Arg Gly Ala Gly
 35 40 45
 Thr Arg Glu Leu Glu Leu Ala Ile Arg Ile Thr Leu Tyr Ala Val Ile
 50 55 60
 30 Phe Leu Met Ser Val Gly Gly Asn Met Leu Ile Ile Val Val Leu Gly
 65 70 75 80
 Leu Ser Arg Arg Leu Arg Thr Val Thr Asn Ala Phe Leu Leu Ser Leu
 85 90 95

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| | | | | |
|----|---|-----|-----|-----|
| | Ala Val Ser Asp Leu Leu Leu Ala Val Ala Cys Met Pro Phe Thr Leu | 100 | 105 | 110 |
| | Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys | 115 | 120 | 125 |
| 5 | Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser | 130 | 135 | 140 |
| | Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu | 145 | 150 | 155 |
| 10 | Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val | 165 | 170 | 175 |
| | Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr | 180 | 185 | 190 |
| | Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg | 195 | 200 | 205 |
| 15 | Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu | 210 | 215 | 220 |
| | Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu | 225 | 230 | 235 |
| 20 | Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp | 245 | 250 | 255 |
| | Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala | 260 | 265 | 270 |
| | Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys | 275 | 280 | 285 |
| 25 | Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu | 290 | 295 | 300 |
| | Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro | 305 | 310 | 315 |
| 30 | Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Lys Arg Met Leu Leu | 325 | 330 | 335 |
| | Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala | 340 | 345 | 350 |
| | Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser | 355 | 360 | 365 |
| 35 | Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys | 370 | 375 | 380 |
| | Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala | | | |

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385 390 395 400
 Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg
 405 410 415
 5 Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser
 420 425 430
 Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly
 435 440 445

(114) INFORMATION FOR SEQ ID NO:113:

- 10 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 34 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

CAGCAGCATG CGCTTCACGC GCTTCTTAGC CCAG

34

(115) INFORMATION FOR SEQ ID NO:114:

- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 33 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:114:

25 AGAAGCGCGT GAAGCGCATG CTGCTGGTGA TCGTT

35

(116) INFORMATION FOR SEQ ID NO:115:

- 30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 33 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:115:

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ATGGAGAAAA GAATCAAAAG AATGTTCTAT ATA

33

(117) INFORMATION FOR SEQ ID NO:116:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:116:

TATATAGAAC ATTCTTTTGA TTCTTTTCTC CAT

33

(118) INFORMATION FOR SEQ ID NO:117:

(i) SEQUENCE CHARACTERISTICS:

- 15 (A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:117:

CGCTCTCTGG CCTTGAAGCG CACGCTCAGC

30

(119) INFORMATION FOR SEQ ID NO:118:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118:

GCTGAGCGTG CGCTTCAAGG CCAGAGAGCG

30

(120) INFORMATION FOR SEQ ID NO:119:

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- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
5 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:
- CCCAGGAAAA AGGTGAAAGT CAAAGTTTTC 30
- 10 (121) INFORMATION FOR SEQ ID NO:120:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
15 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: YES
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:120:
- GAAAACTTTG ACTTTCACCT TTTTCTGGG 30
- 20 (122) INFORMATION FOR SEQ ID NO:121:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 27 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
25 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121:
- GGGGCGCGGG TGAAACGGCT GGTGAGC 27
- 30 (123) INFORMATION FOR SEQ ID NO:122:
- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 27 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:122:

5 GCTCACCAGC CGTTTCACCC GCGCCCC

27

(124) INFORMATION FOR SEQ ID NO:123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:123:

15 CCCCTTGAAA AGCCTAAGAA CTTGGTCATC

30

(125) INFORMATION FOR SEQ ID NO:124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:124:

25 GATGACCAAG TTCTTAGGCT TTTCAAGGGG

30

(126) INFORMATION FOR SEQ ID NO:125:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleic acid

30 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

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(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

GATCTCTAGA ATGAACAGCA CATGTATTGA AG

32

(127) INFORMATION FOR SEQ ID NO:126:

- 5 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: DNA (genomic)

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

CTAGGGTACC CGCTCAAGGA CCTCTAATTC CATAG

35

(128) INFORMATION FOR SEQ ID NO:127:

- 15 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 1296 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

| | |
|--|-----|
| ATGCAGGCGC TTAACATTAC CCCGGAGCAG TTCTCTCGGC TGCTGCGGGA CCACAACCTG | 60 |
| ACGCGGGAGC AGTTCATCGC TCTGTACCGG CTGCGACCGC TCGTCTACAC CCCAGAGCTG | 120 |
| CCGGGACGCG CCAAGCTGGC CCTCGTGCTC ACCGGCGTGC TCATCTTCGC CCTGGCGCTC | 180 |
| 25 TTTGGCAATG CTCTGGTGTT CTACGTGGTG ACCCGCAGCA AGGCCATGCG CACCGTCACC | 240 |
| AACATCTTTA TCTGCTCCTT GGCCTCAGT GACCTGCTCA TCACCTTCTT CTGCATTCCC | 300 |
| GTCACCATGC TCCAGAACAT TTCCGACAAC TGGCTGGGGG GTGCTTTCAT TTGCAAGATG | 360 |
| GTGCCATTTG TCCAGTCTAC CGCTGTTGTG ACAGAAATGC TCACTATGAC CTGCATTGCT | 420 |
| GTGGAAAGGC ACCAGGGACT TGTGCATCCT TTTAAAATGA AGTGGCAATA CACCAACCGA | 480 |

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AGGGCTTTCA CAATGCTAGG TGTGGTCTGG CTGGTGGCAG TCATCGTAGG ATCACCCATG 540
 TGGCACGTGC AACAACTTGA GATCAAATAT GACTTCCTAT ATGAAAAGGA ACACATCTGC 600
 TGCTTAGAAG AGTGGACCAG CCCTGTGCAC CAGAAGATCT ACACCACCTT CATCCTTGTC 660
 ATCCTCTTCC TCCTGCCTCT TATGGTGATG CTTATTCTGT ACAGTAAAAT TGGTTATGAA 720
 5 CTTTGGATAA AGAAAAGAGT TGGGGATGGT TCAGTGCTTC GAAC'TATTCA TGGAAAAGAA 780
 ATGTCCAAAA TAGCCAGGAA GAAGAAACGA GCTAAGATTA TGATGGTGAC AGTGGTGGCT 840
 CTCTTTGCTG TGTGCTGGGC ACCATTCCAT GTTGTCCATA TGATGATTGA ATACAGTAAT 900
 TTTGAAAAGG AATATGATGA TGTCACAATC AAGATGATTT TTGCTATCGT GCAAATTATT 960
 GGATTTTCCA ACTCCATCTG TAATCCCATT GTCTATGCAT TTATGAATGA AAAC'TTCAA 1020
 10 AAAAAATGTTT TGTCTGCAGT TTGTTATTGC ATAGTAAATA AAACCTTCTC TCCAGCACAA 1080
 AGGCATGGAA ATTCAGGAAT TACAATGATG CGGAAGAAAG CAAAGTTTTC CCTCAGAGAG 1140
 AATCCAGTGG AGGAAACCAA AGGAGAAGCA TTCAGTGATG GCAACATTGA AGTCAAATTG 1200
 TGTGAACAGA CAGAGGAGAA GAAAAAGCTC AAACGACATC TTGCTCTCTT TAGGTCTGAA 1260
 CTGGCTGAGA ATTCTCCTTT AGACAGTGGG CATTAA 1296

15 (129) INFORMATION FOR SEQ ID NO:128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 431 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

20 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:128:

Met Gln Ala Leu Asn Ile Thr Pro Glu Gln Phe Ser Arg Leu Leu Arg
 1 5 10 15
 25 Asp His Asn Leu Thr Arg Glu Gln Phe Ile Ala Leu Tyr Arg Leu Arg
 20 25 30
 Pro Leu Val Tyr Thr Pro Glu Leu Pro Gly Arg Ala Lys Leu Ala Leu
 35 40 45
 30 Val Leu Thr Gly Val Leu Ile Phe Ala Leu Ala Leu Phe Gly Asn Ala
 50 55 60
 Leu Val Phe Tyr Val Val Thr Arg Ser Lys Ala Met Arg Thr Val Thr
 65 70 75 80

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Asn | Ile | Phe | Ile | Cys | Ser | Leu | Ala | Leu | Ser | Asp | Leu | Leu | Ile | Thr | Phe | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| | Phe | Cys | Ile | Pro | Val | Thr | Met | Leu | Gln | Asn | Ile | Ser | Asp | Asn | Trp | Leu | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| 5 | Gly | Gly | Ala | Phe | Ile | Cys | Lys | Met | Val | Pro | Phe | Val | Gln | Ser | Thr | Ala | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | Val | Val | Thr | Glu | Met | Leu | Thr | Met | Thr | Cys | Ile | Ala | Val | Glu | Arg | His | |
| | | | 130 | | | | | 135 | | | | 140 | | | | | |
| 10 | Gln | Gly | Leu | Val | His | Pro | Phe | Lys | Met | Lys | Trp | Gln | Tyr | Thr | Asn | Arg | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Arg | Ala | Phe | Thr | Met | Leu | Gly | Val | Val | Trp | Leu | Val | Ala | Val | Ile | Val | |
| | | | | | 165 | | | | | 170 | | | | | | 175 | |
| | Gly | Ser | Pro | Met | Trp | His | Val | Gln | Gln | Leu | Glu | Ile | Lys | Tyr | Asp | Phe | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| 15 | Leu | Tyr | Glu | Lys | Glu | His | Ile | Cys | Cys | Leu | Glu | Glu | Trp | Thr | Ser | Pro | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| | Val | His | Gln | Lys | Ile | Tyr | Thr | Thr | Phe | Ile | Leu | Val | Ile | Leu | Phe | Leu | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| 20 | Leu | Pro | Leu | Met | Val | Met | Leu | Ile | Leu | Tyr | Ser | Lys | Ile | Gly | Tyr | Glu | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Leu | Trp | Ile | Lys | Lys | Arg | Val | Gly | Asp | Gly | Ser | Val | Leu | Arg | Thr | Ile | |
| | | | | 245 | | | | | | 250 | | | | | 255 | | |
| | His | Gly | Lys | Glu | Met | Ser | Lys | Ile | Ala | Arg | Lys | Lys | Lys | Arg | Ala | Lys | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| 25 | Ile | Met | Met | Val | Thr | Val | Val | Ala | Leu | Phe | Ala | Val | Cys | Trp | Ala | Pro | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| | Phe | His | Val | Val | His | Met | Met | Ile | Glu | Tyr | Ser | Asn | Phe | Glu | Lys | Glu | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| 30 | Tyr | Asp | Asp | Val | Thr | Ile | Lys | Met | Ile | Phe | Ala | Ile | Val | Gln | Ile | Ile | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Gly | Phe | Ser | Asn | Ser | Ile | Cys | Asn | Pro | Ile | Val | Tyr | Ala | Phe | Met | Asn | |
| | | | | 325 | | | | | 330 | | | | | | 335 | | |
| | Glu | Asn | Phe | Lys | Lys | Asn | Val | Leu | Ser | Ala | Val | Cys | Tyr | Cys | Ile | Val | |
| | | | | 340 | | | | 345 | | | | | 350 | | | | |
| 35 | Asn | Lys | Thr | Phe | Ser | Pro | Ala | Gln | Arg | His | Gly | Asn | Ser | Gly | Ile | Thr | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| | Met | Met | Arg | Lys | Lys | Ala | Lys | Phe | Ser | Leu | Arg | Glu | Asn | Pro | Val | Glu | |

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| | | | | | |
|---|---|-----|-----|-----|---------|
| | 370 | | 375 | | 380 |
| | Glu Thr Lys Gly Glu Ala Phe Ser Asp Gly Asn Ile Glu Val Lys Leu | | | | |
| | 385 | | 390 | | 395 400 |
| 5 | Cys Glu Gln Thr Glu Glu Lys Lys Lys Leu Lys Arg His Leu Ala Leu | | | | |
| | | 405 | | 410 | 415 |
| | Phe Arg Ser Glu Leu Ala Glu Asn Ser Pro Leu Asp Ser Gly His | | | | |
| | | 420 | 425 | | 430 |

(130) INFORMATION FOR SEQ ID NO:129:

- (i) SEQUENCE CHARACTERISTICS:
- 10 (A) LENGTH: 2040 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:129:

ATGGGCAGCC CCTGGAACGG CAGCGACGGC CCCGAGGGGG CGCGGGAGCC GCCGTGGCCC
60

GCGCTGCCGC CTTGCGACGA GCGCCGCTGC TCGCCCTTTC CCCTGGGGGC GCTGGTGCCG
120

20 GTGACCGCTG TGTGCCTGTG CCTGTTCGTC GTCGGGGTGA GCGGCAACGT GGTGACCGTG
180

ATGCTGATCG GCGCCTACCG GGACATGCGG ACCACCACCA ACTTGTAACCT GGGCAGCATG
240

GCCGTGTCCG ACCTACTCAT CCTGCTCGGG CTGCCGTTTC ACCTGTACCG CCTCTGGCGC
25 300

TCGCGGCCCT GGGTGTTTCG GCGCTGCTC TGCCGCCTGT CCCTCTACGT GGGCGAGGGC
360

TGCACCTACG CCACGCTGCT GCACATGACC GCGCTCAGCG TCGAGCGCTA CCTGGCCATC
30 420

TGCCGCCCCG TCCGCGCCCC CGTCTTGCTC ACCCGGCGCC GCGTCCGCGC GCTCATCGCT
480

GTGCTCTGGG CCGTGGCGCT GCTCTCTGCC GGTCCCTTCT TGTTCCTGGT GGGCGTCGAG
35 540

CAGGACCCCG GCATCTCCGT AGTCCCGGGC CTCAATGGCA CCGCGCGGAT CGCCTCCTCG
600

40 CCTCTCGCCT CGTCGCGGCC TCTCTGGCTC TCGCGGGCGC CACCGCCGTC CCCGCCGTCG

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660
GGGCCCCGAGA CCGCGGAGGC CGCGGCGCTG TTCAGCCGCG AATGCCGGCC GAGCCCCGCG
720
5 CAGCTGGGCG CGCTGCGTGT CATGCTGTGG GTCACCACCG CCTACTTCTT CCTGCCCTTT
780
CTGTGCCTCA GCATCCTCTA CGGGCTCATC GGGCGGGAGC TGTGGAGCAG CCGGCGGCCG
10 840
CTGCGAGGCC CGGCCGCCTC GGGGCGGGAG AGAGGCCACC GGCAGACCAA ACGCGTCCTG
900
15 CGTAAGTGA GCCGCCGTGG TTCCAAAGAC GCCTGCCTGC AGTCCGCCCC GCCGGGGACC
960
GCGCAAACGC TGGGTCCCCT TCCCCTGCTC GCCAGCTCT GGGCGCCGCT TCCAGCTCCC
1020
20 TTTCCTATTT CGATTCCAGC CTCCACCCGC CGGTACTTCC CATCCCCCGA GAAAACCATG
1080
TCCTGTCCCC CAGGAGCTCT GGGGGACCCC AGGGCGCTTT GAGGGTGGGA TCCCCGGATC
25 1140
CGATTCACTA ACCAGCAGTG CTTTTCCAGA GCCTCTGAGA CCAGAAAGGA GAGTTGGTAA
1200
30 TTCTTAATCC AACCACCTGT TAGATGCCAC AAATGAGGAG TCCTCACAGT GCTCTTGAGA
1260
AGACGAGGGA GATTTCATTA AGCTAAAATT TTTTATTTAA TGTTAAGTGA TGCTGAAGGC
1320
35 TAAAGTAAAC CTTGCTCGTA TCAAAAAGTA AAGATTGTGC AGACCTGTTG TAGAATTCTT
1380
TTCAACAGAG AACAGAAAAC TTGTCTCCGA AGTGGGTTTG TGGAAGGAAG CCTGCCAAGG
40 1440
CGGCTTGTTT AGAGAAATTG CTCCTTCTGG TTTATGTCCA GCCTTGATAA CACATATGGG
1500
45 AGCCTACTAT GCAGTTTTAA AGCAAGTATC CATGCAGCCT GCAGCCTGGT CATTTTTTCT
1560
GGGGTGAGGA TCTGCCTAGG TAGAAGTTTT CTCTAATTTA TTTTGCTGTT ACTTGTTATT
1620
50 GCAGATGGTT CCTTGTCGGG GTGGGGGGTT TATTTGCTTC CCAATGCTTT TGTTAATCCC
1680
GGTGCTGTGT CTTATGTTGC AGTGGTGGTG GTTCTGGCAT TTATAATTTG CTGGTTGCCC
55 1740

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TTCCACGTTG GCAGAATCAT TTACATAAAC ACGGAAGATT CGCGGATGAT GTACTTCTCT
 1800

5 CAGTACTTTA ACATCGTCGC TCTGCAACTT TTCTATCTGA GCGCATCTAT CAACCCAATC
 1860

CTCTACAACC TCATTTCAAA GAAGTACAGA GCGGCGGCCT TTAAACTGCT GCTCGCAAGG
 1920

10 AAGTCCAGGC CGAGAGGCTT CCACAGAAGC AGGGACACTG CGGGGGAAGT TGCAGGGGAC
 1980

ACTGGAGGAG ACACGGTGGG CTACACCGAG ACAAGCGCTA ACGTGAAGAC GATGGGATAA
 15 2040

(131) INFORMATION FOR SEQ ID NO:130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 412 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

20 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:130:

25 Met Gly Ser Pro Trp Asn Gly Ser Asp Gly Pro Glu Gly Ala Arg Glu
 1 5 10 15

Pro Pro Trp Pro Ala Leu Pro Pro Cys Asp Glu Arg Arg Cys Ser Pro
 20 25 30

Phe Pro Leu Gly Ala Leu Val Pro Val Thr Ala Val Cys Leu Cys Leu
 35 40 45

30 Phe Val Val Gly Val Ser Gly Asn Val Val Thr Val Met Leu Ile Gly
 50 55 60

Arg Tyr Arg Asp Met Arg Thr Thr Thr Asn Leu Tyr Leu Gly Ser Met
 65 70 75 80

35 Ala Val Ser Asp Leu Leu Ile Leu Leu Gly Leu Pro Phe Asp Leu Tyr
 85 90 95

Arg Leu Trp Arg Ser Arg Pro Trp Val Phe Gly Pro Leu Leu Cys Arg
 100 105 110

Leu Ser Leu Tyr Val Gly Glu Gly Cys Thr Tyr Ala Thr Leu Leu His
 115 120 125

40 Met Thr Ala Leu Ser Val Glu Arg Tyr Leu Ala Ile Cys Arg Pro Leu
 130 135 140

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Arg | Ala | Arg | Val | Leu | Val | Thr | Arg | Arg | Arg | Val | Arg | Ala | Leu | Ile | Ala | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| | Val | Leu | Trp | Ala | Val | Ala | Leu | Leu | Ser | Ala | Gly | Pro | Phe | Leu | Phe | Leu | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| 5 | Val | Gly | Val | Glu | Gln | Asp | Pro | Gly | Ile | Ser | Val | Val | Pro | Gly | Leu | Asn | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| | Gly | Thr | Ala | Arg | Ile | Ala | Ser | Ser | Pro | Leu | Ala | Ser | Ser | Pro | Pro | Leu | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| 10 | Trp | Leu | Ser | Arg | Ala | Pro | Pro | Pro | Ser | Pro | Pro | Ser | Gly | Pro | Glu | Thr | |
| | 210 | | | | | 215 | | | | | | 220 | | | | | |
| | Ala | Glu | Ala | Ala | Ala | Leu | Phe | Ser | Arg | Glu | Cys | Arg | Pro | Ser | Pro | Ala | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Gln | Leu | Gly | Ala | Leu | Arg | Val | Met | Leu | Trp | Val | Thr | Thr | Ala | Tyr | Phe | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| 15 | Phe | Leu | Pro | Phe | Leu | Cys | Leu | Ser | Ile | Leu | Tyr | Gly | Leu | Ile | Gly | Arg | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Glu | Leu | Trp | Ser | Ser | Arg | Arg | Pro | Leu | Arg | Gly | Pro | Ala | Ala | Ser | Gly | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| 20 | Arg | Glu | Arg | Gly | His | Arg | Gln | Thr | Lys | Arg | Val | Leu | Leu | Val | Val | Val | |
| | 290 | | | | | | 295 | | | | | 300 | | | | | |
| | Leu | Ala | Phe | Ile | Ile | Cys | Trp | Leu | Pro | Phe | His | Val | Gly | Arg | Ile | Ile | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| | Tyr | Ile | Asn | Thr | Glu | Asp | Ser | Arg | Met | Met | Tyr | Phe | Ser | Gln | Tyr | Phe | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| 25 | Asn | Ile | Val | Ala | Leu | Gln | Leu | Phe | Tyr | Leu | Ser | Ala | Ser | Ile | Asn | Pro | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| | Ile | Leu | Tyr | Asn | Leu | Ile | Ser | Lys | Lys | Tyr | Arg | Ala | Ala | Ala | Phe | Lys | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| 30 | Leu | Leu | Leu | Ala | Arg | Lys | Ser | Arg | Pro | Arg | Gly | Phe | His | Arg | Ser | Arg | |
| | 370 | | | | | | 375 | | | | | 380 | | | | | |
| | Asp | Thr | Ala | Gly | Glu | Val | Ala | Gly | Asp | Thr | Gly | Gly | Asp | Thr | Val | Gly | |
| | 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| | Tyr | Thr | Glu | Thr | Ser | Ala | Asn | Val | Lys | Thr | Met | Gly | | | | | |
| | | | | | 405 | | | | | 410 | | | | | | | |

35 (132) INFORMATION FOR SEQ ID NO:131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1344 base pairs

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(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131:

ATGGAGCTGC TAAAGCTGAA CCGGAGCGTG CAGGGAACCG GACCCGGGCC GGGGGCTTCC
60
CTGTGCCGCC CGGGGGCGCC TCTCCTCAAC AGCAGCAGTG TGGGCAACCT CAGCTGCGAG
120
10 CCCCCTCGCA TTCGCGGAGC CGGGACACGA GAATTGGAGC TGGCCATTAG AATCACTCTT
180
TACGCAGTGA TCTTCCTGAT GAGCGTTGGA GGAAATATGC TCATCATCGT GGTCTTGGGA
240
CTGAGCCGCC GCCTGAGGAC TGTCACCAAT GCCTTCCTCC TCTCACTGGC AGTCAGCGAC
15 300
CTCCTGCTGG CTGTGGCTTG CATGCCCTTC ACCCTCCTGC CCAATCTCAT GGGCACATTC
360
ATCTTTGGCA CCGTCATCTG CAAGGCGGTT TCCTACCTCA TGGGGGTGTC TGTGAGTGTG
420
20 TCCACGCTAA GCCTCGTGGC CATCGCACTG GAGCGATATA GCGCCATCTG CCGACCACTG
480
CAGGCACGAG TGTGGCAGAC GCGCTCCAC GCGGCTCGCG TGATTGTAGC CACGTGGCTG
540
CTGTCCGGAC TACTCATGGT GCCCTACCCC GTGTACACTG TCGTGCAACC AGTGGGGCCT
25 600
CGTGTGCTGC AGTGCGTGCA TCGCTGGCCC AGTGCGCGGG TCCGCCAGAC CTGGTCCGTA
660
CTGCTGCTTC TGCTCTTGTT CTTCATCCCA GGTGTGGTTA TGGCCGTGGC CTACGGGCTT
720
30 ATCTCTCGCG AGCTCTACTT AGGGCTTCGC TTTGACGGCG ACAGTGACAG CGACAGCCAA
780
AGCAGGGTCC GAAACCAAGG CGGGCTGCCA GGGGCTGTTC ACCAGAACGG GCGTTGCCGG
840
CCTGAGACTG GCGCGGTTGG CAAAGACAGC GATGGCTGCT ACGTGCAACT TCCACGTTCC
35 900
CGGCCTGCCC TGGAGCTGAC GCGCTGACG GCTCCTGGGC CGGGATCCGG CTCCCGGCCC

- 100 -

960

ACCCAGGCCA AGCTGCTGGC TAAGAAGCGC GTGAAACGAA TGTTGCTGGT GATCGTTGTG
1020

CTTTTTTTTC TGTGTTGGTT GCCAGTTTAT AGTGCCAACA CGTGGCGCGC CTTTGATGGC
5 1080

CCGGGTGCAC ACCGAGCACT CTCGGGTGCT CCTATCTCCT TCATTCACTT GCTGAGCTAC
1140

GCCTCGGCCT GTGTCAACCC CCTGGTCTAC TGCTTCATGC ACCGTCGCTT TCGCCAGGCC
1200

10 TGCCTGGAAA CTTGCGCTCG CTGCTGCCCC CGGCCTCCAC GAGCTCGCCC CAGGGCTCTT
1260

CCCATGAGG ACCCTCCCAC TCCCTCCATT GCTTCGCTGT CCAGGCTTAG CTACACCACC
1320

15 ATCAGCACAC TGGGCCCTGG CTGA
1344

(133) INFORMATION FOR SEQ ID NO:132:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 447 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:132:

| | | | | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| 25 | Met | Glu | Leu | Leu | Lys | Leu | Asn | Arg | Ser | Val | Gln | Gly | Thr | Gly | Pro | Gly | 1 | 5 | 10 | 15 |
| | Pro | Gly | Ala | Ser | Leu | Cys | Arg | Pro | Gly | Ala | Pro | Leu | Leu | Asn | Ser | Ser | 20 | 25 | 30 | |
| | Ser | Val | Gly | Asn | Leu | Ser | Cys | Glu | Pro | Pro | Arg | Ile | Arg | Gly | Ala | Gly | 35 | 40 | 45 | |
| 30 | Thr | Arg | Glu | Leu | Glu | Leu | Ala | Ile | Arg | Ile | Thr | Leu | Tyr | Ala | Val | Ile | 50 | 55 | 60 | |
| | Phe | Leu | Met | Ser | Val | Gly | Gly | Asn | Met | Leu | Ile | Ile | Val | Val | Leu | Gly | 65 | 70 | 75 | 80 |
| 35 | Leu | Ser | Arg | Arg | Leu | Arg | Thr | Val | Thr | Asn | Ala | Phe | Leu | Leu | Ser | Leu | 85 | 90 | 95 | |
| | Ala | Val | Ser | Asp | Leu | Leu | Leu | Ala | Val | Ala | Cys | Met | Pro | Phe | Thr | Leu | | | | |

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| | 100 | 105 | 110 |
|----|--|-----|-----|
| | Leu Pro Asn Leu Met Gly Thr Phe Ile Phe Gly Thr Val Ile Cys Lys 115 120 125 | | |
| 5 | Ala Val Ser Tyr Leu Met Gly Val Ser Val Ser Val Ser Thr Leu Ser 130 135 140 | | |
| | Leu Val Ala Ile Ala Leu Glu Arg Tyr Ser Ala Ile Cys Arg Pro Leu 145 150 155 160 | | |
| | Gln Ala Arg Val Trp Gln Thr Arg Ser His Ala Ala Arg Val Ile Val 165 170 175 | | |
| 10 | Ala Thr Trp Leu Leu Ser Gly Leu Leu Met Val Pro Tyr Pro Val Tyr 180 185 190 | | |
| | Thr Val Val Gln Pro Val Gly Pro Arg Val Leu Gln Cys Val His Arg 195 200 205 | | |
| 15 | Trp Pro Ser Ala Arg Val Arg Gln Thr Trp Ser Val Leu Leu Leu Leu 210 215 220 | | |
| | Leu Leu Phe Phe Ile Pro Gly Val Val Met Ala Val Ala Tyr Gly Leu 225 230 235 240 | | |
| | Ile Ser Arg Glu Leu Tyr Leu Gly Leu Arg Phe Asp Gly Asp Ser Asp 245 250 255 | | |
| 20 | Ser Asp Ser Gln Ser Arg Val Arg Asn Gln Gly Gly Leu Pro Gly Ala 260 265 270 | | |
| | Val His Gln Asn Gly Arg Cys Arg Pro Glu Thr Gly Ala Val Gly Lys 275 280 285 | | |
| 25 | Asp Ser Asp Gly Cys Tyr Val Gln Leu Pro Arg Ser Arg Pro Ala Leu 290 295 300 | | |
| | Glu Leu Thr Ala Leu Thr Ala Pro Gly Pro Gly Ser Gly Ser Arg Pro 305 310 315 320 | | |
| | Thr Gln Ala Lys Leu Leu Ala Lys Lys Arg Val Lys Arg Met Leu Leu 325 330 335 | | |
| 30 | Val Ile Val Val Leu Phe Phe Leu Cys Trp Leu Pro Val Tyr Ser Ala 340 345 350 | | |
| | Asn Thr Trp Arg Ala Phe Asp Gly Pro Gly Ala His Arg Ala Leu Ser 355 360 365 | | |
| 35 | Val Ala Pro Ile Ser Phe Ile His Leu Leu Ser Tyr Ala Ser Ala Cys 370 375 380 | | |
| | Val Asn Pro Leu Val Tyr Cys Phe Met His Arg Arg Phe Arg Gln Ala 385 390 395 400 | | |

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Cys Leu Glu Thr Cys Ala Arg Cys Cys Pro Arg Pro Pro Arg Ala Arg
 405 410 415

Pro Arg Ala Leu Pro Asp Glu Asp Pro Pro Thr Pro Ser Ile Ala Ser
 420 425 430

5 Leu Ser Arg Leu Ser Tyr Thr Thr Ile Ser Thr Leu Gly Pro Gly
 435 440 445

(134) INFORMATION FOR SEQ ID NO:133:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 1014 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:133:

15 ATGAACAGCA CATGTATTGA AGAACAGCAT GACCTGGATC ACTATTTGTT TCCCATTGTT 60
 TACATCTTTG TGATTATAGT CAGCATTCCA GCCAATATTG GATCTCTGTG TGTGTCTTTC 120
 CTGCAAGCAA AGAAGGAAAG TGAAC TAGGA ATTTACCTCT TCAGTTTGTC ACTATCAGAT 180
 TTA CTCTATG CATTA ACTCT CCCTTTATGG ATTGATTATA CTTGGAATAA AGACA ACTGG 240
 ACTTTCTCTC CTGCCTTGTG CAAAGGGAGT GCTTTTCTCA TGTACATGAA TTTTACAGC 300
 20 AGCACAGCAT TCCTCACCTG CATTGCCGTT GATCGGTATT TGGCTGTTGT CTACCCTTTG 360
 AAGTTTTTTT TCCTAAGGAC AAGAAGATTT GCACTCATGG TCAGCCTGTC CATCTGGATA 420
 TTGGAACCA TCTTCAATGC TGTCATGTTG TGGGAAGATG AAACAGTTGT TGAATATTGC 480
 GATGCCGAAA AGTCTAATTT TACTTTATGC TATGACAAAT ACCCTTTAGA GAAATGGCAA 540
 ATCAACCTCA ACTTGTTTCAG GACGTGTACA GGCTATGCAA TACCTTTGGT CACCATCCTG 600
 25 ATCTGTAACC GGAAAGTCTA CCAAGCTGTG CGGCACAATA AAGCCACGGA AAACAAGGAA 660
 AAGAAGAGAA TCAAAAACT ACTTGTCAGC ATCACAGTTA CTTTTGTCTT ATGCTTTACT 720
 CCCTTTCATG TGATGTTGCT GATTCGCTGC ATTTTAGAGC ATGCTGTGAA CTTCGAAGAC 780
 CACAGCAATT CTGGGAAGCG AACTTACACA ATGTATAGAA TCACGGTTGC ATTAACAAGT 840
 TTAAATTGTG TTGCTGATCC AATTCTGTAC TGTTTTGTTA CCGAAACAGG AAGATATGAT 900
 > 30 ATGTGGAATA TATTAAAATT CTGCACTGGG AGGTGTAATA CATCACAAAG ACAAAGAAAA 960
 CGCATACTTT CTGTGTCTAC AAAAGATACT ATGGAATTAG AGGTCCTTGA GTAG 1014

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(135) INFORMATION FOR SEQ ID NO:134:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 337 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:134:

| | | | | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 10 | Met | Asn | Ser | Thr | Cys | Ile | Glu | Glu | Gln | His | Asp | Leu | Asp | His | Tyr | Leu | 1 | 5 | 10 | 15 |
| | Phe | Pro | Ile | Val | Tyr | Ile | Phe | Val | Ile | Ile | Val | Ser | Ile | Pro | Ala | Asn | 20 | 25 | 30 | |
| | Ile | Gly | Ser | Leu | Cys | Val | Ser | Phe | Leu | Gln | Ala | Lys | Lys | Glu | Ser | Glu | 35 | 40 | 45 | |
| 15 | Leu | Gly | Ile | Tyr | Leu | Phe | Ser | Leu | Ser | Leu | Ser | Asp | Leu | Leu | Tyr | Ala | 50 | 55 | 60 | |
| | Leu | Thr | Leu | Pro | Leu | Trp | Ile | Asp | Tyr | Thr | Trp | Asn | Lys | Asp | Asn | Trp | 65 | 70 | 75 | 80 |
| 20 | Thr | Phe | Ser | Pro | Ala | Leu | Cys | Lys | Gly | Ser | Ala | Phe | Leu | Met | Tyr | Met | 85 | 90 | 95 | |
| | Asn | Phe | Tyr | Ser | Ser | Thr | Ala | Phe | Leu | Thr | Cys | Ile | Ala | Val | Asp | Arg | 100 | 105 | 110 | |
| | Tyr | Leu | Ala | Val | Val | Tyr | Pro | Leu | Lys | Phe | Phe | Phe | Leu | Arg | Thr | Arg | 115 | 120 | 125 | |
| 25 | Arg | Phe | Ala | Leu | Met | Val | Ser | Leu | Ser | Ile | Trp | Ile | Leu | Glu | Thr | Ile | 130 | 135 | 140 | |
| | Phe | Asn | Ala | Val | Met | Leu | Trp | Glu | Asp | Glu | Thr | Val | Val | Glu | Tyr | Cys | 145 | 150 | 155 | 160 |
| 30 | Asp | Ala | Glu | Lys | Ser | Asn | Phe | Thr | Leu | Cys | Tyr | Asp | Lys | Tyr | Pro | Leu | 165 | 170 | 175 | |
| | Glu | Lys | Trp | Gln | Ile | Asn | Leu | Asn | Leu | Phe | Arg | Thr | Cys | Thr | Gly | Tyr | 180 | 185 | 190 | |
| | Ala | Ile | Pro | Leu | Val | Thr | Ile | Leu | Ile | Cys | Asn | Arg | Lys | Val | Tyr | Gln | 195 | 200 | 205 | |
| 35 | Ala | Val | Arg | His | Asn | Lys | Ala | Thr | Glu | Asn | Lys | Glu | Lys | Lys | Arg | Ile | 210 | 215 | 220 | |

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Lys Lys Leu Leu Val Ser Ile Thr Val Thr Phe Val Leu Cys Phe Thr
 225 230 235 240
 Pro Phe His Val Met Leu Leu Ile Arg Cys Ile Leu Glu His Ala Val
 245 250 255
 5 Asn Phe Glu Asp His Ser Asn Ser Gly Lys Arg Thr Tyr Thr Met Tyr
 260 265 270
 Arg Ile Thr Val Ala Leu Thr Ser Leu Asn Cys Val Ala Asp Pro Ile
 275 280 285
 10 Leu Tyr Cys Phe Val Thr Glu Thr Gly Arg Tyr Asp Met Trp Asn Ile
 290 295 300
 Leu Lys Phe Cys Thr Gly Arg Cys Asn Thr Ser Gln Arg Gln Arg Lys
 305 310 315 320
 Arg Ile Leu Ser Val Ser Thr Lys Asp Thr Met Glu Leu Glu Val Leu
 325 330 335
 15 Glu

(136) INFORMATION FOR SEQ ID NO:135:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 999 base pairs
 20 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

25 ATGGTGAACT CCACCCACCG TGGGATGCAC ACTTCTCTGC ACCTCTGGAA CCGCAGCAGT
 60
 TACAGACTGC ACAGCAATGC CAGTGAGTCC CTTGGAAAAG GCTACTCTGA TGGAGGGTGC
 120
 TACGAGCAAC TTTTGTCTC TCCTGAGGTG TTTGTGACTC TGGGTGTCAT CAGCTTGTTG
 30 180
 GAGAATATCT TAGTGATTGT GGCAATAGCC AAGAACAAGA ATCTGCATTC ACCCATGTAC
 240
 TTTTTCATCT GCAGCTTGGC TGTGGCTGAT ATGCTGGTGA GCGTTTCAAA TGGATCAGAA
 300
 35 ACCATTATCA TCACCCTATT AAACAGTACA GATACGGATG CACAGAGTTT CACAGTGAAT
 360

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ATTGATAATG TCATTGACTC GGTGATCTGT AGCTCCTTGC TTGCATCCAT TTGCAGCCTG
420

CTTTCAATTG CAGTGGACAG GTACTTTACT ATCTTCTATG CTCTCCAGTA CCATAACATT
480

5 ATGACAGTTA AGCGGGTTGG GATCAGCATA AGTTGTATCT GGGCAGCTTG CACGGTTTCA
540

GGCATTTTGT TCATCATTTA CTCAGATAGT AGTGCTGTCA TCATCTGCCT CATCACCATG
600

10 TTCTTCACCA TGCTGGCTCT CATGGCTTCT CTCTATGTCC ACATGTTTCCT GATGGCCAGG
660

CTTCACATTA AGAGGATTGC TGTCTCCCC GGCAGTGGTG CCATCCGCCA AGGTGCCAAT
720

ATGAAGGGAA AAATTACCTT GACCATCCTG ATTGGCGTCT TTGTTGTCTG CTGGGCCCCA
780

15 TTCTTCCTCC ACTTAATATT CTACATCTCT TGTCTCAGA ATCCATATTG TGTGTGCTTC
840

ATGTCTCACT TTAAGTTGTA TCTCATACTG ATCATGTGTA ATTCAATCAT CGATCCTCTG
900

20 ATTTATGCAC TCCGGAGTCA AGAACTGAGG AAAACCTTCA AAGAGATCAT CTGTTGCTAT
960

CCCCTGGGAG GCCTTTGTGA CTTGTCTAGC AGATATTAA
999

(137) INFORMATION FOR SEQ ID NO:136:

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 332 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:136:

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Val | Asn | Ser | Thr | His | Arg | Gly | Met | His | Thr | Ser | Leu | His | Leu | Trp |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |
| Asn | Arg | Ser | Ser | Tyr | Arg | Leu | His | Ser | Asn | Ala | Ser | Glu | Ser | Leu | Gly |
| | | 20 | | | | | 25 | | | | | 30 | | | |
| Lys | Gly | Tyr | Ser | Asp | Gly | Gly | Cys | Tyr | Glu | Gln | Leu | Phe | Val | Ser | Pro |
| | | 35 | | | | | 40 | | | | | 45 | | | |

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Glu | Val | Phe | Val | Thr | Leu | Gly | Val | Ile | Ser | Leu | Leu | Glu | Asn | Ile | Leu | |
| | 50 | | | | | | 55 | | | | | 60 | | | | | |
| | Val | Ile | Val | Ala | Ile | Ala | Lys | Asn | Lys | Asn | Leu | His | Ser | Pro | Met | Tyr | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| 5 | Phe | Phe | Ile | Cys | Ser | Leu | Ala | Val | Ala | Asp | Met | Leu | Val | Ser | Val | Ser | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| | Asn | Gly | Ser | Glu | Thr | Ile | Ile | Ile | Thr | Leu | Leu | Asn | Ser | Thr | Asp | Thr | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| 10 | Asp | Ala | Gln | Ser | Phe | Thr | Val | Asn | Ile | Asp | Asn | Val | Ile | Asp | Ser | Val | |
| | | | 115 | | | | | 120 | | | | | 125 | | | | |
| | Ile | Cys | Ser | Ser | Leu | Leu | Ala | Ser | Ile | Cys | Ser | Leu | Leu | Ser | Ile | Ala | |
| | 130 | | | | | | 135 | | | | | 140 | | | | | |
| | Val | Asp | Arg | Tyr | Phe | Thr | Ile | Phe | Tyr | Ala | Leu | Gln | Tyr | His | Asn | Ile | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| 15 | Met | Thr | Val | Lys | Arg | Val | Gly | Ile | Ser | Ile | Ser | Cys | Ile | Trp | Ala | Ala | |
| | | | | | 165 | | | | | 170 | | | | | 175 | | |
| | Cys | Thr | Val | Ser | Gly | Ile | Leu | Phe | Ile | Ile | Tyr | Ser | Asp | Ser | Ser | Ala | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| 20 | Val | Ile | Ile | Cys | Leu | Ile | Thr | Met | Phe | Phe | Thr | Met | Leu | Ala | Leu | Met | |
| | | | 195 | | | | | 200 | | | | | 205 | | | | |
| | Ala | Ser | Leu | Tyr | Val | His | Met | Phe | Leu | Met | Ala | Arg | Leu | His | Ile | Lys | |
| | | | 210 | | | | 215 | | | | | 220 | | | | | |
| | Arg | Ile | Ala | Val | Leu | Pro | Gly | Thr | Gly | Ala | Ile | Arg | Gln | Gly | Ala | Asn | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| 25 | Met | Lys | Gly | Lys | Ile | Thr | Leu | Thr | Ile | Leu | Ile | Gly | Val | Phe | Val | Val | |
| | | | | | 245 | | | | | 250 | | | | | 255 | | |
| | Cys | Trp | Ala | Pro | Phe | Phe | Leu | His | Leu | Ile | Phe | Tyr | Ile | Ser | Cys | Pro | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| 30 | Gln | Asn | Pro | Tyr | Cys | Val | Cys | Phe | Met | Ser | His | Phe | Asn | Leu | Tyr | Leu | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| | Ile | Leu | Ile | Met | Cys | Asn | Ser | Ile | Ile | Asp | Pro | Leu | Ile | Tyr | Ala | Leu | |
| | 290 | | | | | | 295 | | | | | 300 | | | | | |
| | Arg | Ser | Gln | Glu | Leu | Arg | Lys | Thr | Phe | Lys | Glu | Ile | Ile | Cys | Cys | Tyr | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| 35 | Pro | Leu | Gly | Gly | Leu | Cys | Asp | Leu | Ser | Ser | Arg | Tyr | | | | | |
| | | | | | 325 | | | | | 330 | | | | | | | |

(138) INFORMATION FOR SEQ ID NO:137:

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

GCCAATATGA AGGGAAAAAT TACCTTGACC ATC
33

10 (137) INFORMATION FOR SEQ ID NO:138:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:138:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T
31

20 (140) INFORMATION FOR SEQ ID NO:139:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1842 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

ATGGGGCCCA CCCTAGCGGT TCCCACCCCC TATGGCTGTA TTGGCTGTAA GCTACCCCAG 60
CCAGAATACC CACCGGCTCT AATCATCTTT ATGTTCTGCG CGATGGTTAT CACCATCGTT 120
30 GTAGACCTAA TCGGCAACTC CATGGTCATT TTGGCTGTGA CGAAGAACAA GAAGCTCCGG 180
AATTCTGGCA ACATCTTCGT GGTCAGTCTC TCTGTGGCCG ATATGCTGGT GGCCATCTAC 240
CCATACCCTT TGATGCTGCA TGCCATGTCC ATTGGGGGCT GGGATCTGAG CCAGTTACAG 300
TGCCAGATGG TCGGGTTCAT CACAGGGCTG AGTGTGGTCG GCTCCATCTT CAACATCGTG 360

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| | | |
|----|--|------|
| | GCAATCGCTA TCAACCGTTA CTGCTACATC TGCCACAGCC TCCAGTACGA ACGGATCTTC | 420 |
| | AGTGTGCGCA ATACCTGCAT CTACCTGGTC ATCACCTGGA TCATGACCGT CCTGGCTGTC | 480 |
| | CTGCCCCAACA TGTACATTGG CACCATCGAG TACGATCCTC GCACCTACAC CTGCATCTTC | 540 |
| | AACTATCTGA ACAACCTGT CTTCCTGTT ACCATCGTCT GCATCCACTT CGTCCTCCCT | 600 |
| 5 | CTCCTCATCG TGGGTTTCTG CTACGTGAGG ATCTGGACCA AAGTGCTGGC GGCCCGTGAC | 660 |
| | CCTGCAGGGC AGAATCCTGA CAACCAACTT GCTGAGGTTT GCAATTTTCT AACCATGTTT | 720 |
| | GTGATCTTCC TCCTCTTTGC AGTGTGCTGG TGCCCTATCA ACGTGCTCAC TGTCTTGGTG | 780 |
| | GCTGTCAGTC CGAAGGAGAT GGCAGGCAAG ATCCCCAACT GGCTTTATCT TGCAGCCTAC | 840 |
| | TTCATAGCCT ACTTCAACAG CTGCCTCAAC GCTGTGATCT ACGGGCTCCT CAATGAGAAT | 900 |
| 10 | TTCCGAAGAG AATACTGGAC CATCTTCCAT GCTATGCGGC ACCCTATCAT ATTCTTCCCT | 960 |
| | GGCCTCATCA GTGATATTCG TGAGATGCAG GAGGCCCGTA CCCTGGCCCG CGCCCGTGCC | 1020 |
| | CATGCTCGCG ACCAAGCTCG TGAACAAGAC CGTGCCCATG CCTGTCCTGC TGTGGAGGAA | 1080 |
| | ACCCCGATGA ATGTCCGGAA TGTTCATTA CCTGGTGATG CTGCAGCTGG CCACCCCGAC | 1140 |
| | CGTGCCTCTG GCCACCCTAA GCCCCATTCC AGATCCTCCT CTGCCTATCG CAAATCTGCC | 1200 |
| 15 | TCTACCCACC ACAAGTCTGT CTTTAGCCAC TCCAAGGCTG CCTCTGGTCA CCTCAAGCCT | 1260 |
| | GTCTCTGGCC ACTCCAAGCC TGCCCTCTGGT CACCCCAAGT CTGCCACTGT CTACCCTAAG | 1320 |
| | CCTGCCTCTG TCCATTTCAA GGGTGACTCT GTCCATTTCA AGGGTGACTC TGTCCATTTT | 1380 |
| | AAGCCTGACT CTGTTTATTT CAAGCCTGCT TCCAGCAACC CCAAGCCCAT CACTGGCCAC | 1440 |
| | CATGTCTCTG CTGGCAGCCA CTCCAAGTCT GCCTTCAGTG CTGCCACCAG CCACCCTAAA | 1500 |
| 20 | CCCATCAAGC CAGCTACCAG CCATGCTGAG CCCACCACTG CTGACTATCC CAAGCCTGCC | 1560 |
| | ACTACCAGCC ACCCTAAGCC CGCTGCTGCT GACAACCCTG AGCTCTCTGC CTCCCATTGC | 1620 |
| | CCCGAGATCC CTGCCATTGC CCACCCTGTG TCTGACGACA GTGACCTCCC TGAGTCGGCC | 1680 |
| | TCTAGCCCTG CCGCTGGGCC CACCAAGCCT GCTGCCAGCC AGCTGGAGTC TGACACCATC | 1740 |
| | GCTGACCTTC CTGACCCTAC TGTAGTCACT ACCAGTACCA ATGATTACCA TGATGTCGTG | 1800 |
| 25 | GTTGTTGATG TTGAAGATGA TCCTGATGAA ATGGCTGTGT GA | 1842 |

(141) INFORMATION FOR SEQ ID NO:140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 613 amino acids

(B) TYPE: amino acid

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(C) STRANDEDNESS:

(D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

| | | | | | |
|----|---|-----|-----|-----|-----|
| 5 | Met Gly Pro Thr Leu Ala Val Pro Thr Pro Tyr Gly Cys Ile Gly Cys | 1 | 5 | 10 | 15 |
| | Lys Leu Pro Gln Pro Glu Tyr Pro Pro Ala Leu Ile Ile Phe Met Phe | 20 | 25 | 30 | |
| 10 | Cys Ala Met Val Ile Thr Ile Val Val Asp Leu Ile Gly Asn Ser Met | 35 | 40 | 45 | |
| | Val Ile Leu Ala Val Thr Lys Asn Lys Lys Leu Arg Asn Ser Gly Asn | 50 | 55 | 60 | |
| | Ile Phe Val Val Ser Leu Ser Val Ala Asp Met Leu Val Ala Ile Tyr | 65 | 70 | 75 | 80 |
| 15 | Pro Tyr Pro Leu Met Leu His Ala Met Ser Ile Gly Gly Trp Asp Leu | 85 | 90 | 95 | |
| | Ser Gln Leu Gln Cys Gln Met Val Gly Phe Ile Thr Gly Leu Ser Val | 100 | 105 | 110 | |
| 20 | Val Gly Ser Ile Phe Asn Ile Val Ala Ile Ala Ile Asn Arg Tyr Cys | 115 | 120 | 125 | |
| | Tyr Ile Cys His Ser Leu Gln Tyr Glu Arg Ile Phe Ser Val Arg Asn | 130 | 135 | 140 | |
| | Thr Cys Ile Tyr Leu Val Ile Thr Trp Ile Met Thr Val Leu Ala Val | 145 | 150 | 155 | 160 |
| 25 | Leu Pro Asn Met Tyr Ile Gly Thr Ile Glu Tyr Asp Pro Arg Thr Tyr | 165 | 170 | 175 | |
| | Thr Cys Ile Phe Asn Tyr Leu Asn Asn Pro Val Phe Thr Val Thr Ile | 180 | 185 | 190 | |
| 30 | Val Cys Ile His Phe Val Leu Pro Leu Leu Ile Val Gly Phe Cys Tyr | 195 | 200 | 205 | |
| | Val Arg Ile Trp Thr Lys Val Leu Ala Ala Arg Asp Pro Ala Gly Gln | 210 | 215 | 220 | |
| | Asn Pro Asp Asn Gln Leu Ala Glu Val Arg Asn Phe Leu Thr Met Phe | 225 | 230 | 235 | 240 |
| 35 | Val Ile Phe Leu Leu Phe Ala Val Cys Trp Cys Pro Ile Asn Val Leu | 245 | 250 | 255 | |

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Thr | Val | Leu | Val | Ala | Val | Ser | Pro | Lys | Glu | Met | Ala | Gly | Lys | Ile | Pro | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| | Asn | Trp | Leu | Tyr | Leu | Ala | Ala | Tyr | Phe | Ile | Ala | Tyr | Phe | Asn | Ser | Cys | |
| | | | 275 | | | | | 280 | | | | | 285 | | | | |
| 5 | Leu | Asn | Ala | Val | Ile | Tyr | Gly | Leu | Leu | Asn | Glu | Asn | Phe | Arg | Arg | Glu | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | Tyr | Trp | Thr | Ile | Phe | His | Ala | Met | Arg | His | Pro | Ile | Ile | Phe | Phe | Pro | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| 10 | Gly | Leu | Ile | Ser | Asp | Ile | Arg | Glu | Met | Gln | Glu | Ala | Arg | Thr | Leu | Ala | |
| | | | | | 325 | | | | | 330 | | | | | 335 | | |
| | Arg | Ala | Arg | Ala | His | Ala | Arg | Asp | Gln | Ala | Arg | Glu | Gln | Asp | Arg | Ala | |
| | | | | 340 | | | | | 345 | | | | | 350 | | | |
| | His | Ala | Cys | Pro | Ala | Val | Glu | Glu | Thr | Pro | Met | Asn | Val | Arg | Asn | Val | |
| | | | 355 | | | | | 360 | | | | | 365 | | | | |
| 15 | Pro | Leu | Pro | Gly | Asp | Ala | Ala | Ala | Gly | His | Pro | Asp | Arg | Ala | Ser | Gly | |
| | | 370 | | | | 375 | | | | | | 380 | | | | | |
| | His | Pro | Lys | Pro | His | Ser | Arg | Ser | Ser | Ser | Ala | Tyr | Arg | Lys | Ser | Ala | |
| | 385 | | | | | 390 | | | | | 395 | | | | | 400 | |
| 20 | Ser | Thr | His | His | Lys | Ser | Val | Phe | Ser | His | Ser | Lys | Ala | Ala | Ser | Gly | |
| | | | | | 405 | | | | | 410 | | | | | 415 | | |
| | His | Leu | Lys | Pro | Val | Ser | Gly | His | Ser | Lys | Pro | Ala | Ser | Gly | His | Pro | |
| | | | | 420 | | | | | 425 | | | | | 430 | | | |
| | Lys | Ser | Ala | Thr | Val | Tyr | Pro | Lys | Pro | Ala | Ser | Val | His | Phe | Lys | Gly | |
| | | | 435 | | | | 440 | | | | | | 445 | | | | |
| 25 | Asp | Ser | Val | His | Phe | Lys | Gly | Asp | Ser | Val | His | Phe | Lys | Pro | Asp | Ser | |
| | | 450 | | | | | 455 | | | | | 460 | | | | | |
| | Val | His | Phe | Lys | Pro | Ala | Ser | Ser | Asn | Pro | Lys | Pro | Ile | Thr | Gly | His | |
| | 465 | | | | 470 | | | | | | 475 | | | | | 480 | |
| 30 | His | Val | Ser | Ala | Gly | Ser | His | Ser | Lys | Ser | Ala | Phe | Ser | Ala | Ala | Thr | |
| | | | | | 485 | | | | | 490 | | | | | 495 | | |
| | Ser | His | Pro | Lys | Pro | Ile | Lys | Pro | Ala | Thr | Ser | His | Ala | Glu | Pro | Thr | |
| | | | | 500 | | | | | 505 | | | | | 510 | | | |
| | Thr | Ala | Asp | Tyr | Pro | Lys | Pro | Ala | Thr | Thr | Ser | His | Pro | Lys | Pro | Ala | |
| | | | 515 | | | | | 520 | | | | | 525 | | | | |
| 35 | Ala | Ala | Asp | Asn | Pro | Glu | Leu | Ser | Ala | Ser | His | Cys | Pro | Glu | Ile | Pro | |
| | | 530 | | | | | 535 | | | | | 540 | | | | | |
| | Ala | Ile | Ala | His | Pro | Val | Ser | Asp | Asp | Ser | Asp | Leu | Pro | Glu | Ser | Ala | |

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| | | | | | | | |
|---|-----------------|---------------------|-----------------|-----------------|-----|-----|-----|
| | 545 | | 550 | | 555 | | 560 |
| | Ser Ser Pro Ala | Ala Gly Pro Thr Lys | Pro Ala Ala Ser | Gln Leu Glu | | | |
| | | 565 | | 570 | | 575 | |
| 5 | Ser Asp Thr Ile | Ala Asp Leu Pro | Asp Pro Thr Val | Val Thr Thr Ser | | | |
| | | 580 | | 585 | | 590 | |
| | Thr Asn Asp Tyr | His Asp Val Val | Val Val Asp Val | Glu Asp Asp Pro | | | |
| | | 595 | | 600 | | 605 | |
| | Asp Glu Met Ala | Val | | | | | |
| | | 610 | | | | | |

10 (142) INFORMATION FOR SEQ ID NO:141:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1842 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

15

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:141:

| | | | | | | | |
|----|------------|------------|------------|------------|------------|------------|-----|
| | ATGGGGCCCA | CCCTAGCGGT | TCCCACCCCC | TATGGCTGTA | TTGGCTGTAA | GCTACCCCAG | 60 |
| | CCAGAATACC | CACCGGCTCT | AATCATCTTT | ATGTTCTGCG | CGATGGTTAT | CACCATCGTT | 120 |
| 20 | GTAGACCTAA | TCGGCAACTC | CATGGTCATT | TTGGCTGTGA | CGAAGAACAA | GAAGCTCCGG | 180 |
| | AATTCTGGCA | ACATCTTCGT | GGTCAGTCTC | TCTGTGGCCG | ATATGCTGGT | GGCCATCTAC | 240 |
| | CCATACCCTT | TGATGCTGCA | TGCCATGTCC | ATTGGGGGCT | GGGATCTGAG | CCAGTTACAG | 300 |
| | TGCCAGATGG | TCGGGTTCAT | CACAGGGCTG | AGTGTGGTCG | GCTCCATCTT | CAACATCGTG | 360 |
| | GCAATCGCTA | TCAACCGTTA | CTGCTACATC | TGCCACAGCC | TCCAGTACGA | ACGGATCTTC | 420 |
| 25 | AGTGTGCGCA | ATACCTGCAT | CTACCTGGTC | ATCACCTGGA | TCATGACCGT | CCTGGCTGTC | 480 |
| | CTGCCCCACA | TGTACATTGG | CACCATCGAG | TACGATCCTC | GCACCTACAC | CTGCATCTTC | 540 |
| | AACTATCTGA | ACAACCCTGT | CTTCACTGTT | ACCATCGTCT | GCATCCACTT | CGTCCTCCCT | 600 |
| | CTCCTCATCG | TGGGTTTCTG | CTACGTGAGG | ATCTGGACCA | AAGTGCTGGC | GGCCCGTGAC | 660 |
| | CCTGCAGGGC | AGAATCCTGA | CAACCAACTT | GCTGAGGTTC | GCAATAAACT | AACCATGTTT | 720 |
| 30 | GTGATCTTCC | TCCTCTTTGC | AGTGTGCTGG | TGCCCTATCA | ACGTGCTCAC | TGTCTTGGTG | 780 |
| | GCTGTCTAGT | CGAAGGAGAT | GGCAGGCAAG | ATCCCCAACT | GGCTTTATCT | TGCAGCCTAC | 840 |

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TTCATAGCCT ACTTCAACAG CTGCCTCAAC GCTGTGATCT ACGGGCTCCT CAATGAGAAT 900
 TTCCGAAGAG AATACTGGAC CATCTTCCAT GCTATGCGGC ACCCTATCAT ATTCTTCTCT 960
 GGCCTCATCA GTGATATTCG TGAGATGCAG GAGGCCCGTA CCCTGGCCCCG CGCCCGTGCC 1020
 CATGCTCGCG ACCAAGCTCG TGAACAAGAC CGTGCCCATG CCTGTCCTGC TGTGGAGGAA 1080
 5 ACCCCGATGA ATGTCCGGAA TGTTCATTA CTTGGTGATG CTGCAGCTGG CCACCCCGAC 1140
 CGTGCTCTG GCCACCCTAA GCCCCATTCC AGATCCTCCT CTGCCTATCG CAAATCTGCC 1200
 TCTACCCACC ACAAGTCTGT CTTTAGCCAC TCCAAGGCTG CCTCTGGTCA CCTCAAGCCT 1260
 GTCTCTGGCC ACTCCAAGCC TGCCTCTGGT CACCCCAAGT CTGCCACTGT CTACCCTAAG 1320
 CCTGCCTCTG TCCATTTCAA GGCTGACTCT GTCCATTTC AAGGTGACTC TGTCCATTTC 1380
 10 AAGCCTGACT CTGTTCAATT CAAGCCTGCT TCCAGCAACC CCAAGCCCAT CACTGGCCAC 1440
 CATGTCTCTG CTGGCAGCCA CTCCAAGTCT GCCTTCAATG CTGCCACCAG CCACCCTAAA 1500
 CCCATCAAGC CAGCTACCAG CCATGCTGAG CCCACCACTG CTGACTATCC CAAGCCTGCC 1560
 ACTACCAGCC ACCCTAAGCC CGCTGCTGCT GACAACCCTG AGCTCTCTGC CTCCCATTGC 1620
 CCCGAGATCC CTGCCATTGC CCACCCTGTG TCTGACGACA GTGACCTCCC TGAGTCGGCC 1680
 15 TCTAGCCCTG CCGCTGGGCC CACCAAGCCT GCTGCCAGCC AGCTGGAGTC TGACACCATC 1740
 GCTGACCTTC CTGACCCTAC TGTAGTCACT ACCAGTACCA ATGATTACCA TGATGTCGTG 1800
 GTTGTGATG TTGAAGATGA TCCTGATGAA ATGGCTGTGT GA 1842

(143) INFORMATION FOR SEQ ID NO:142:

- (i) SEQUENCE CHARACTERISTICS:
 20 (A) LENGTH: 613 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS:
 (D) TOPOLOGY: not relevant

(ii) MOLECULE TYPE: protein

- 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:

Met Gly Pro Thr Leu Ala Val Pro Thr Pro Tyr Gly Cys Ile Gly Cys
 1 5 10 15

Lys Leu Pro Gln Pro Glu Tyr Pro Pro Ala Leu Ile Ile Phe Met Phe
 20 25 30

30 Cys Ala Met Val Ile Thr Ile Val Val Asp Leu Ile Gly Asn Ser Met
 35 40 45

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| | | | | | | | | | | | | | | | | | |
|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| | Val | Ile | Leu | Ala | Val | Thr | Lys | Asn | Lys | Lys | Leu | Arg | Asn | Ser | Gly | Asn | |
| | 50 | | | | | | 55 | | | | | 60 | | | | | |
| | Ile | Phe | Val | Val | Ser | Leu | Ser | Val | Ala | Asp | Met | Leu | Val | Ala | Ile | Tyr | |
| | 65 | | | | | 70 | | | | | 75 | | | | | 80 | |
| 5 | Pro | Tyr | Pro | Leu | Met | Leu | His | Ala | Met | Ser | Ile | Gly | Gly | Trp | Asp | Leu | |
| | | | | | 85 | | | | | 90 | | | | | 95 | | |
| | Ser | Gln | Leu | Gln | Cys | Gln | Met | Val | Gly | Phe | Ile | Thr | Gly | Leu | Ser | Val | |
| | | | | 100 | | | | | 105 | | | | | 110 | | | |
| 10 | Val | Gly | Ser | Ile | Phe | Asn | Ile | Val | Ala | Ile | Ala | Ile | Asn | Arg | Tyr | Cys | |
| | | 115 | | | | | | 120 | | | | | 125 | | | | |
| | Tyr | Ile | Cys | His | Ser | Leu | Gln | Tyr | Glu | Arg | Ile | Phe | Ser | Val | Arg | Asn | |
| | 130 | | | | | | 135 | | | | | 140 | | | | | |
| | Thr | Cys | Ile | Tyr | Leu | Val | Ile | Thr | Trp | Ile | Met | Thr | Val | Leu | Ala | Val | |
| | 145 | | | | | 150 | | | | | 155 | | | | | 160 | |
| 15 | Leu | Pro | Asn | Met | Tyr | Ile | Gly | Thr | Ile | Glu | Tyr | Asp | Pro | Arg | Thr | Tyr | |
| | | | | 165 | | | | | | 170 | | | | | 175 | | |
| | Thr | Cys | Ile | Phe | Asn | Tyr | Leu | Asn | Asn | Pro | Val | Phe | Thr | Val | Thr | Ile | |
| | | | | 180 | | | | | 185 | | | | | 190 | | | |
| 20 | Val | Cys | Ile | His | Phe | Val | Leu | Pro | Leu | Leu | Ile | Val | Gly | Phe | Cys | Tyr | |
| | | 195 | | | | | | 200 | | | | | 205 | | | | |
| | Val | Arg | Ile | Trp | Thr | Lys | Val | Leu | Ala | Ala | Arg | Asp | Pro | Ala | Gly | Gln | |
| | | 210 | | | | | 215 | | | | | 220 | | | | | |
| | Asn | Pro | Asp | Asn | Gln | Leu | Ala | Glu | Val | Arg | Asn | Lys | Leu | Thr | Met | Phe | |
| | 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| 25 | Val | Ile | Phe | Leu | Leu | Phe | Ala | Val | Cys | Trp | Cys | Pro | Ile | Asn | Val | Leu | |
| | | | | 245 | | | | | | 250 | | | | | 255 | | |
| | Thr | Val | Leu | Val | Ala | Val | Ser | Pro | Lys | Glu | Met | Ala | Gly | Lys | Ile | Pro | |
| | | | | 260 | | | | | 265 | | | | | 270 | | | |
| 30 | Asn | Trp | Leu | Tyr | Leu | Ala | Ala | Tyr | Phe | Ile | Ala | Tyr | Phe | Asn | Ser | Cys | |
| | | 275 | | | | | | 280 | | | | | 285 | | | | |
| | Leu | Asn | Ala | Val | Ile | Tyr | Gly | Leu | Leu | Asn | Glu | Asn | Phe | Arg | Arg | Glu | |
| | | 290 | | | | | 295 | | | | | 300 | | | | | |
| | Tyr | Trp | Thr | Ile | Phe | His | Ala | Met | Arg | His | Pro | Ile | Ile | Phe | Phe | Ser | |
| | 305 | | | | | 310 | | | | | 315 | | | | | 320 | |
| 35 | Gly | Leu | Ile | Ser | Asp | Ile | Arg | Glu | Met | Gln | Glu | Ala | Arg | Thr | Leu | Ala | |
| | | | | 325 | | | | | | 330 | | | | | 335 | | |
| | Arg | Ala | Arg | Ala | His | Ala | Arg | Asp | Gln | Ala | Arg | Glu | Gln | Asp | Arg | Ala | |

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| | 340 | | 345 | | 350 | |
|----|---|---|-----|-----|-----|-----|
| | His Ala Cys Pro Ala Val | Glu Glu Thr Pro Met Asn Val Arg Asn Val | | | | |
| | 355 | 360 | | 365 | | |
| 5 | Pro Leu Pro Gly Asp Ala Ala Ala Gly His Pro Asp Arg Ala Ser Gly | | | | | |
| | 370 | 375 | | 380 | | |
| | His Pro Lys Pro His Ser Arg Ser Ser Ser Ala Tyr Arg Lys Ser Ala | | | | | |
| | 385 | 390 | | 395 | 400 | |
| | Ser Thr His His Lys Ser Val Phe Ser His Ser Lys Ala Ala Ser Gly | | | | | |
| | | 405 | | 410 | 415 | |
| 10 | His Leu Lys Pro Val Ser Gly His Ser Lys Pro Ala Ser Gly His Pro | | | | | |
| | | 420 | | 425 | 430 | |
| | Lys Ser Ala Thr Val Tyr Pro Lys Pro Ala Ser Val His Phe Lys Ala | | | | | |
| | | 435 | | 440 | 445 | |
| 15 | Asp Ser Val His Phe Lys Gly Asp Ser Val His Phe Lys Pro Asp Ser | | | | | |
| | | 450 | | 455 | 460 | |
| | Val His Phe Lys Pro Ala Ser Ser Asn Pro Lys Pro Ile Thr Gly His | | | | | |
| | | 465 | | 470 | 475 | 480 |
| | His Val Ser Ala Gly Ser His Ser Lys Ser Ala Phe Asn Ala Ala Thr | | | | | |
| | | 485 | | 490 | 495 | |
| 20 | Ser His Pro Lys Pro Ile Lys Pro Ala Thr Ser His Ala Glu Pro Thr | | | | | |
| | | 500 | | 505 | 510 | |
| | Thr Ala Asp Tyr Pro Lys Pro Ala Thr Thr Ser His Pro Lys Pro Ala | | | | | |
| | | 515 | | 520 | 525 | |
| 25 | Ala Ala Asp Asn Pro Glu Leu Ser Ala Ser His Cys Pro Glu Ile Pro | | | | | |
| | | 530 | | 535 | 540 | |
| | Ala Ile Ala His Pro Val Ser Asp Asp Ser Asp Leu Pro Glu Ser Ala | | | | | |
| | | 545 | | 550 | 555 | 560 |
| | Ser Ser Pro Ala Ala Gly Pro Thr Lys Pro Ala Ala Ser Gln Leu Glu | | | | | |
| | | 565 | | 570 | 575 | |
| 30 | Ser Asp Thr Ile Ala Asp Leu Pro Asp Pro Thr Val Val Thr Thr Ser | | | | | |
| | | 580 | | 585 | 590 | |
| | Thr Asn Asp Tyr His Asp Val Val Val Asp Val Glu Asp Asp Pro | | | | | |
| | | 595 | | 600 | 605 | |
| 35 | Asp Glu Met Ala Val | | | | | |
| | 610 | | | | | |

(144) INFORMATION FOR SEQ ID NO:143:

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- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:143:

GCTGAGGTTC GCAATAAACT AACCATGTTT GTG

33

(145) INFORMATION FOR SEQ ID NO:144:

- 10 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:144:

CTCCTTCGGT CCTCCTATCG TTGTCAGAAG T

31

(146) INFORMATION FOR SEQ ID NO:145:

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

25 (iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:145:

TTAGATATCG GGGCCCACCC TAGCGGT

33

(147) INFORMATION FOR SEQ ID NO:146:

- 30 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

- 116 -

(iv) ANTI-SENSE: YES

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:146:

GGTACCCCCA CAGCCATTTC ATCAGGATC

33

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International Bureau(43) International Publication Date
20 April 2000 (20.04.2000)

PCT

(10) International Publication Number
WO 00/22131 A3(51) International Patent Classification⁷: C12N 15/16,
C07K 14/72(71) Applicant (for all designated States except US): ARENA
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(21) International Application Number: PCT/US99/24065

(72) Inventors; and

(22) International Filing Date: 13 October 1999 (13.10.1999)

(75) Inventors/Applicants (for US only): BEHAN, Dominic,
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(25) Filing Language: English

(26) Publication Language: English

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| 60/109,213 | 20 November 1998 (20.11.1998) | US |
| 60/110,060 | 27 November 1998 (27.11.1998) | US |
| 60/120,416 | 16 February 1999 (16.02.1999) | US |
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| 60/137,127 | 28 May 1999 (28.05.1999) | US |
| 60/137,131 | 28 May 1999 (28.05.1999) | US |
| 60/141,448 | 30 June 1999 (30.06.1999) | US |
| 60/151,114 | 27 August 1999 (27.08.1999) | US |
| 60/152,524 | 3 September 1999 (03.09.1999) | US |
| 60/156,653 | 29 September 1999 (29.09.1999) | US |
| 60/156,633 | 29 September 1999 (29.09.1999) | US |
| 60/156,555 | 29 September 1999 (29.09.1999) | US |
| 60/156,634 | 29 September 1999 (29.09.1999) | US |
| 60/157,280 | 1 October 1999 (01.10.1999) | US |
| 60/157,294 | 1 October 1999 (01.10.1999) | US |
| 60/157,281 | 1 October 1999 (01.10.1999) | US |
| 60/157,293 | 1 October 1999 (01.10.1999) | US |
| 60/157,282 | 1 October 1999 (01.10.1999) | US |
| 09/417,044 | 12 October 1999 (12.10.1999) | US |
| 09/416,760 | 12 October 1999 (12.10.1999) | US |

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erty Place, Philadelphia, PA 19103 (US).(81) Designated States (national): AE, AL, AM, AT, AU, AZ,
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DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
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(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

(88) Date of publication of the international search report:
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(CIP) to earlier application:

| | |
|----------|------------------------------|
| US | 09/170,496 (CIP) |
| Filed on | 13 October 1998 (13.10.1998) |

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: NON-ENDOGENOUS, CONSTITUTIVELY ACTIVATED HUMAN G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The invention disclosed in this patent document relates to transmembrane receptors, more particularly to a human G protein-coupled receptor for which the endogenous ligand is unknown ("orphan GPCR receptors"), and most particularly to mutated (non-endogenous) versions of the human GPCRs for evidence of constitutive activity.

WO 00/22131 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/24065

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/16 C07K14/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 97 21731 A (NEW ENGLAND MEDICAL CENTER INC) 19 June 1997 (1997-06-19) page 18, line 16 - line 26 figures 2,3 | 1-4 |
| A | SCHEER A. ET AL.: "CONSTITUTIVELY ACTIVE G PROTEIN-COUPLED RECEPTORS: POTENTIAL MECHANISMS OF RECEPTOR ACTIVATION" JOURNAL OF RECEPTOR AND SIGNAL TRANSDUCTION RESEARCH, vol. 17, no. 1/03, 1997, pages 57-73, XP000867531 ISSN: 1079-9893 the whole document | 1-4 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

2 March 2000

Date of mailing of the international search report

14 06. 2000

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Fax: (+31-70) 340-3016

Authorized officer

Mandl, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/24065

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | WO 98 38217 A (HERRICK DAVIS KATHARINE ;TEITLER MILT (US); EGAN CHRISTINA C (US)) 3 September 1998 (1998-09-03) figure 4 --- | 1-4 |
| A | KJELSBORG M. A. ET AL.: "CONSTITUTIVE ACTIVATION OF THE ALPHA1B-ADRENERGIC RECEPTOR BY ALL AMINO ACID SUBSTITUTIONS AT A SINGLE SITE" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 267, no. 3, 25 January 1992 (1992-01-25), pages 1430-1433, XP002911764 ISSN: 0021-9258 the whole document --- | 1-4 |
| P,A | PAUWELS P. J. ET AL.: "REVIEW:AMINO ACID DOMAINS INVOLVED IN CONSTITUTIVE ACTIVATION OF G-PROTEIN-COUPLED RECEPTORS" MOLECULAR NEUROBIOLOGY, vol. 17, no. 1/03, 1998, pages 109-135, XP000866477 ISSN: 0893-7648 the whole document --- | 1-4 |
| P,A | WO 99 24569 A (ONO PHARMACEUTICAL CO ;HAGA HISANORI (JP); NAKADE SHINJI (JP); FUK) 20 May 1999 (1999-05-20) SEQ.IDs. 1-3 ----- | 1-4 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/24065

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-4

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-4

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hARE-3(F313K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

2. Claims: 5-8

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hARE-4(V233K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

3. Claims: 9-12

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hARE-5(A240K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

4. Claims: 13-16

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hGPCR14(L257K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

5. Claims: 17-20

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hGPCR27(C283K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

6. Claims: 21-24

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hARE-1(E232K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

7. Claims: 25-28

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hARE-2(G285K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

8. Claims: 29-32

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hPPR1(L239K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

9. Claims: 33-36

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hG2A(K232A); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

10. Claims: 37-40

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hRUP3(L224K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

11. Claims: 41-44

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hRUP5(A236K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

12. Claims: 45-48

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hRUP6(N267K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

13. Claims: 49-52

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hRUP7(A302K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

14. Claims: 53-56

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hCHN4(V236K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

15. Claims: 57-60

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hMC4(A244K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

16. Claims: 61-64

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hCHN3(S284K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

17. Claims: 65-68.

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hCHN6(L352K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

18. Claims: 69-72

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled receptor comprising hCHN8(N235K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

19. Claims: 73-76

A cDNA encoding a non-endogenous, constitutively activated

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

version of a human G-protein-coupled receptor comprising hH9(F236K); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

20. Claims: 77-80

A cDNA encoding a non-endogenous, constitutively activated version of a human G-protein-coupled AT1 receptor selected from the group consisting of hAT1(F239K), hAT1(N111A), hAT1(AT2K255IC3) and hAT1 (A243+); the receptor encoded by said cDNA; a plasmid comprising said cDNA; and a host cell comprising said plasmid.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/24065

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | AU 715611 B | 03-02-2000 |
| | | AU 1334397 A | 03-07-1997 |
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